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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ENDOTHELIAL CELL EXPRESSION PATTERNS**

(57) Abstract: To gain a better understanding of tumor angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived from normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and tumor-derived endothelium revealed 79 differentially expressed genes, including 46 that were specifically elevated in tumor-associated endothelium. Experiments with representative genes from this group demonstrated that most were similarly expressed in the endothelium of primary lung, breast, brain, and pancreatic cancers as well as in metastatic lesions of the liver. These results demonstrate that neoplastic and normal endothelium in humans are distinct at the molecular level, and have significant implications for the development of anti-angiogenic therapies in the future.

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ENDOTHELIAL CELL EXPRESSION PATTERNS

- [01] This application claims the benefit of provisional applications serial numbers 60/222,599 filed August 2, 2000, 60/224,360 filed August 11, 2000, and 60/282,850 filed April 11, 2001, the disclosures of which are expressly incorporated herein.
- [02] The U.S. government retains certain rights in the invention by virtue of the provisions of National Institutes of Health grants CA57345 and CA43460, which supported this work.

TECHNICAL FIELD OF THE INVENTION

- [03] This invention is related to the area of angiogenesis and anti-angiogenesis. In particular, it relates to genes which are characteristically expressed in tumor endothelial and normal endothelial cells.

BACKGROUND OF THE INVENTION

- [04] It is now widely recognized that tumors require a blood supply for expansive growth. This recognition has stimulated a profusion of research on tumor angiogenesis, based on the idea that the vasculature in tumors represents a potential therapeutic target. However, several basic questions about tumor endothelium remain unanswered. For example, are vessels of tumors qualitatively different from normal vessels of the same tissue? What is the relationship of tumor endothelium to endothelium of healing wounds or other physiological or pathological forms of angiogenesis? The answers to these questions critically impact on the potential for new therapeutic approaches to inhibit angiogenesis in a specific manner.

- [05] There is a continuing need in the art to characterize the vasculature of tumors relative to normal vasculature so that any differences can be exploited for therapeutic and diagnostic benefits.
- [06] One technique which can be used to characterize gene expression, or more precisely gene transcription, is termed serial analysis of gene expression (SAGE). Briefly, the SAGE approach is a method for the rapid quantitative and qualitative analysis of mRNA transcripts based upon the isolation and analysis of short defined sequence tags (SAGE Tags) corresponding to expressed genes. Each Tag is a short nucleotide sequences (9-17 base pairs in length) from a defined position in the transcript. In the SAGE method, the Tags are dimerized to reduce bias inherent in cloning or amplification reactions. (See, US Patent 5,695,937) SAGE is particularly suited to the characterization of genes associated with vasculature stimulation or inhibition because it is capable of detecting rare sequences, evaluating large numbers of sequences at one time, and to provide a basis for the identification of previously unknown genes.

SUMMARY OF THE INVENTION

- [07] One embodiment of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an intact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[08] According to another embodiment of the invention a method of inhibiting neoangiogenesis is provided. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a subject in need thereof. Neoangiogenesis is consequently inhibited. The subject may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, may have psoriasis, for example.

[09] Another aspect of the invention is a method of inhibiting tumor growth. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a human subject bearing a tumor. The growth of the tumor is consequently inhibited.

[10] Still another aspect of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an intact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[11] According to still another aspect of the invention an isolated and purified human transmembrane protein is provided. The protein is selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively.

- [12] Yet another aspect of the invention is an isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The isolated and purified nucleic acid molecule may optionally comprise a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.
- [13] Still another aspect of the invention is a recombinant host cell which comprises a nucleic acid molecule. The nucleic acid molecule comprises a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The recombinant host cell optionally comprises a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.
- [14] According to one embodiment of the invention a method is provided for inducing an immune response in a mammal. A nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: , respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal. Optionally the coding sequence is shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271.
- [15] According to yet another embodiment of the invention a method of inducing an immune response in a mammal is provided. A purified human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271, respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal.

[16] Another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with an isolated and purified human transmembrane protein selected from the group consisting of 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271. The isolated and purified human transmembrane protein is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271 respectively. Binding of the molecule comprising an antibody variable region to the human transmembrane protein is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

[17] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a cell comprising a human transmembrane protein selected from the group consisting of 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232. The cell is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232, respectively. Binding of the molecule comprising an antibody variable region to the cell is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

[18] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a human transmembrane protein selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27,

28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275. Binding of a test compound to the human transmembrane protein is determined. A test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

[19] Another embodiment of the present invention is a soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, 250, and 271 respectively. The soluble forms lack transmembrane domains. The soluble form may consist of an extracellular domain of the human transmembrane protein.

[20] Also provided by the present invention is a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[21] Another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[22] According to still another aspect of the invention a method of identifying regions of neoangiogenesis in a patient is provided. A molecule comprising an antibody variable region which specifically binds to an

extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250, and 271, respectively, is administered to a patient. The molecule is bound to a detectable moiety. The detectable moiety is detected in the patient, thereby identifying neoangiogenesis.

[23] According to another aspect of the invention a method is provided for inducing an immune response to tumor endothelial cells in a patient. A mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 13, 17, 19, 22, and 30 as shown in SEQ ID NO: 291, 293, 299, 295, 303, 297, 301, 305, and 307, is administered to a patient in need thereof. An immune response to a human TEM protein is consequently induced.

[24] Still another embodiment of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neo-angiogenesis in the patient.

[25] Still another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 and 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, is administered to the patient. Neoangiogenesis in the patient consequently inhibited.

[26] Yet another aspect of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is

contacted with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

[27] Also provided by the present invention is a method of promoting neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, is administered to a patient in need of neoangiogenesis. Neoangiogenesis in the patient is consequently stimulated.

[28] One embodiment of the invention provides a method of promoting neoangiogenesis in a patient. A nucleic acid molecule encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, is administered to a patient in need of neoangiogenesis. The TEM protein is consequently expressed and neoangiogenesis in the patient is stimulated.

[29] Another embodiment of the invention provides a method of screening for neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: : 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively, is detected in a body fluid collected from the patient. Detection of the TEM protein indicates neoangiogenesis in the patient.

[30] Another aspect of the invention is a method of screening for neoangiogenesis in a patient. A nucleic acid encoding a TEM protein

selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 is detected in a body fluid collected from the patient. The nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264. Detection of the TEM protein indicates neoangiogenesis in the patient.

[31] Yet another embodiment of the invention is an isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. The nucleic acid molecule optionally comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288. The nucleic acid may be maintained in a recombinant host cell.

[32] The present invention also provides an isolated and purified NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[33] The present invention further provides an isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[34] An additional embodiment of the present invention is a method of inhibiting neoangiogenesis. An effective amount of a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289 is administered to a subject in need thereof. Neoangiogenesis is thereby inhibited.

[35] A still further embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM genes selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: : 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, are contacted with a test compound. Expression of said one or more TEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Test compounds which increase expression can be identified as candidates for promoting wound healing.

[36] Yet another embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. The amount of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the amount of one or more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Alternatively, a test compound which increases the amount of one or more TEM proteins in said cells is identified as a candidate drug for treating wound healing.

[37] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. Activity of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the activity of one more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Optionally the cells are endothelial cells. If a test compound increases the activity of one more TEM proteins in said cells it can be identified as a candidate drug for treating wound healing.

[38] An additional aspect of the invention is a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expression construct which encodes one or more TEM proteins selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively. Proliferation of said cells is determined. A test compound which inhibits proliferation of said cells is identified as a candidate drug for treating patients bearing tumors. A test compound which stimulates

proliferation of said cells is identified as a candidate drug for promoting neoangiogenesis, such as for use in wound healing.

[39] Another embodiment of the invention provides a method to identify candidate drugs for treating tumors. Cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, are contacted with a test compound. Expression of said one or more NEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it increases expression of said one or more NEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[40] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. The amount of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[41] An additional aspect of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. Activity of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating

tumors if it increases the activity of said one or more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[42] Still another embodiment of the invention provides a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expression construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. Proliferation of said cells is determined. A test compound which stimulates proliferation of said cells is identified as a candidate drug for treating patients bearing tumors.

[43] Another aspect of the invention is a method for identifying endothelial cells. One or more antibodies which bind specifically to a TEM or NEM protein selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with a population of cells. Cells in the population which have bound to said antibodies are detected. Cells which are bound to said antibodies are identified as endothelial cells. Optionally cells which have bound to said antibodies are isolated from cells which have not bound.

[44] Still another aspect of the invention is a method for identifying endothelial cells. One or more nucleic acid hybridization probes which are complementary to a TEM or NEM gene nucleic acid sequence selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16,

17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with nucleic acids of a population of cells. Nucleic acids which have specifically hybridized to said nucleic acid hybridization probes are detected. Cells whose nucleic acids specifically hybridized are identified as endothelial cells.

[45] Yet another embodiment of the invention is a method of inhibiting neoangiogenesis. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 17, and 19, as shown in SEQ ID NO: 291, 293, 299, 295, 297, and 301, respectively, is administered to a subject in need thereof. Neoangiogenesis is thereby inhibited. The subject may be a mouse, may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[46] These and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with reagents and methods for detection, diagnosis, therapy, and drug screening pertaining to neoangiogenesis and pathological processes involving or requiring neoangiogenesis.

BRIEF DESCRIPTION OF THE DRAWINGS

[47] Fig. 1A-1B. vWF expression in colorectal cancers. vWF (red stain) was detected in vessels by in situ hybridization. At low power magnification (Fig. 1.A) vessels were often surrounded by a perivascular cuff of viable cells

(red arrows), with a ring of necrotic cells evident at the periphery (black arrows). At high power magnification (Fig. 1.B) the expression of vWF (red) was clearly localized to the vessels. Sections were counterstained with methyl green.

- [48] Fig. 2A-2D. Purification of Endothelial Cells (ECs) from human normal and malignant tissue. (Fig. 2A) Vessels (red) of frozen sections were stained by immunofluorescence with the P1H12 monoclonal antibody (Chemicon, Temecula, CA) and detected using a biotinylated goat anti-mouse IgG secondary antibody followed by rhodamine-linked streptavidin. The region stained is from within the lamina propria of normal colonic mucosa. Note that the larger vessels (arrowheads) and capillaries (arrows) are positive, and staining of hematopoietic cells was undetectable. E-cadherin positive epithelial cells (green) at the edge of the crypt were simultaneously visualized using a rabbit polyclonal antibody (Santa Cruz, Santa Cruz, CA), followed by a goat anti-rabbit IgG secondary antibody labelled with alexa (Molecular Probes, Eugene, OR). Sections were imaged at 60X magnification using confocal microscopy. (Fig. 2.B) To isolate pure populations from collagenase dispersed tissues, the epithelial and hematopoietic cell fractions were sequentially removed by negative selection with magnetic beads. The remaining cells were stained with P1H12 and ECs were isolated by positive selection with magnetic beads. (Fig. 2.C) RT-PCR analysis used to assess the purity of the EC preparations. Semiquantitative PCR analysis was performed on cDNA generated either directly from colorectal cancer tissue (unfractionated tumor) or from purified ECs isolated from normal colonic mucosa (normal EC fraction) or colorectal cancer (tumor EC fraction). PCR amplification of the epithelial specific marker cytokeratin 20 (CK20), demonstrated its expression was limited to the unfractionated tumor. Two endothelial specific markers, vWF and VE-cadherin (VE-Cad) showed robust amplification only in the endothelial fractions, validating the purity and enrichment protocol shown in (Fig. 2.B). The ubiquitous housekeeping enzyme GAPDH was observed in all samples.

No signal was detected in the no-template (NT) control. cDNA templates were diluted 1:10, 1:100, 1:1000, 1:4000, and 1:40,000 as indicated by the declining wedge. (Fig. 2.D) The relative expression level of select genes was determined by measuring the tag abundance from several SAGE libraries combined into four groups. The first was composed of ~193,000 tags from the two in vivo-derived EC preparations (Endothelial Cell Fraction) while the second contained a single library of ~57,000 tags containing macrophages and other leukocytes derived from the negative selection (Hematopoietic Fraction). The fourth library contained ~401,000 tags from cultured HUVEC and HMVEC (Endothelial Cells in Culture), and the fourth consisted of ~748,000 tags from 6 colon cancer cell lines in culture (Epithelial Cells). After normalization, the library with the highest tag number for each marker was given a value of 100%, and the corresponding relative expression levels of the remaining 3 libraries was plotted on the ordinate. Note the high level of CD31 present on hematopoietic cells, the likely cause of the impurity of the initial endothelial selection, compared with the selectivity of PIH12.

- [49] Fig. 3A- 3E). Expression of Pan-Endothelial Markers (PEMs) is limited to ECs. The endothelial origin of PEMs identified by SAGE was confirmed using a highly sensitive in situ hybridization assay. Localization of novel PEMs to the ECs was demonstrated by examining two representative PEMs, PEM3 (Fig. 3A) and PEM6 (Fig. 3B) in lung cancer and colon cancer, respectively. Hevin expression was readily detected in the ECs of a colon tumor (Fig. 3C) despite its low level of expression in cultured ECs. Expression of VEGFR2 was readily detectable in the ECs of both normal (Fig. 3D) and malignant colon tissue (Fig. 3E).
- [50] Fig. 4A-4J. Expression of Tumor Endothelial Markers (TEMs). (Fig. 4A) RT-PCR analysis confirmed the tumor specific expression of selected novel TEMs. Semiquantitative PCR analysis was performed on cDNA generated either from purified epithelial cells as a negative control (Control) or from purified ECs isolated from normal colonic mucosa (Normal ECs) or

colorectal cancer (Tumor ECs) from two different patients. Two endothelial specific markers, vWF and PEM6 showed robust amplification only in the endothelial fractions whereas the ubiquitous housekeeping enzyme GAPDH was observed in all samples. TEM1 (BSC-TEM1), TEM 17 (BSC-TEM7) and TEM22 (BSC-TEM9) were specifically expressed in tumor compared to normal ECs. The cDNA template was diluted 1:10, 1:100, 1:1000, and 1:10,000 as indicated by the declining wedge. (Fig. 4 B- 4J) The endothelial origin of TEMs identified by SAGE was confirmed using in situ hybridization as in Fig 3. Expression of TEM 1 (BSC-TEM1) (Fig. 4 B) and TEM17 (BSC-TEM7) (Fig. 4 C) was demonstrated to be highly specific to the ECs in colorectal cancers; sections were imaged in the absence of a counterstain to show the complete lack of detectable expression in the non-endothelial cells of the tumor. Expression of TEM17 (BSC-TEM7) in ECs was demonstrated in a metastatic liver lesion from a primary colorectal cancer (Fig. 4 D), a lung (Fig. 4 E), breast (Fig. 4 F), pancreatic (Fig. 4 G) and brain cancer (Fig. 4 H), as well as in a sarcoma (Fig. 4 I). TEM 17 (BSC-TEM7) was also localized to vessels during normal physiological angiogenesis of the corpus luteum (Fig. 4 J).

DETAILED DESCRIPTION OF THE INVENTION

[51] We identified 46 human genes that were expressed at significantly higher levels (> 10-fold) in tumor endothelium than in normal endothelium, and 33 genes that were expressed at significantly lower levels in human tumor versus normal endothelium. See Tables 2 and 4, respectively. Most of these genes were either not expressed or expressed at relatively low levels in Endothelial Cells (ECs) maintained in culture. Moreover, we identified 93 genes which are expressed in both normal and tumor human endothelium. Interestingly, the tumor endothelium genes were expressed in all tumors tested, regardless of its tissue or organ source. Most tumor endothelium genes were also expressed in corpus luteum and wounds.

[52] As the work has progressed, we have refined and classified our original 46 tumor endothelial markers. We have named these markers TEMs and renumbered them consecutively by the prevalence of their tags in our SAGE analysis. Originally we had not used a consecutive numbering system. Our non-consecutive numbering system has been renamed as BSC-TEMs. For most of the original 46 SAGE Tags, we now provide full-length nucleic acid and protein sequence. In some cases, the sequences were obtained through the public databases, in others the sequences were obtained by cloning and through the use of gene prediction tools. In some cases, we found SAGE Tags corresponding to genes having different splice variants or with known polymorphisms. For example, in one case the SAGE Tag BSC-TEM3 has been found to hybridize to an alternatively spliced form of the transcript encoding BSC-TEM7. The proteins encoded by the two transcripts are the same; therefore they are cumulatively called TEM7. A highly related sequence was found via homology searches, BSC-TEM7R. This paralog sequence is now called TEM3. See Table 2, which follows, showing tumor endothelial markers by order of prevalence (except for TEM 3). Column 1 indicates the prevalence number. Column 2 indicates the *original nomenclature*. Column 3 indicates the short tags. Column 4 indicates the long tags. Column 5 indicates the accession number in GenBank. Column 6 indicates the sequence identifiers for the short tag, the long tag, the full nucleic acid, and the protein. Column 7 provides a functional description, which is expanded below in the text.

TEM1	BSC- TEM1	GGGGCTGCC CA	GGGGCTGCCCAGCT GA	NM020404	SEQ ID NO : 94, 309, 195, 196	tumor endothelial marker 1 precursor
TEM2	BSC- TEM2	GATCTCCGT GT			SEQ ID NO: 95, 197, 198	sapiens tumor endothelial marker 2 (BSC-TEM2) mRNA/mouse Ras, dexamethasone-induced 1 (RASD1), mRNA
TEM3	BSC- TEM7 R				SEQ ID NO: 199, 200	human ortholog of mouse paralog of mouse TEM-7
TEM4		CTTCTTTGA G	CTTCTTTGAGTTT AA	AB034203	SEQ ID NO: 97, 311, 201, 202	Homo sapiens dickkopf-3 (DKK-3) mRNA,
TEM5	BSC- TEM4	TATTAACCT C	TATTAACCTCTTTG GA		SEQ ID NO: 98, 312, 203, 204	Tumor endothelial marker 4
TEM6		CAGGAGACC CC	CAGGAGACCCAGG CCC	X57766	SEQ ID NO: 99, 314, 205, 206	Human stromelysin-3 mRNA.
TEM7		GGAAATGTC AA	GGAAATGTCAGCAA GTA	BC002576	SEQ ID NO: 100, 315, 207, 208	matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase)

TEM 8		CCTGGTTCA GT			SEQ ID NO:101, 316, 209, 210	HeyL transcription factor
TEM 9	BSC- TEM5	TTTTAAGAA C	TTTTAAGAACTCGG GT		SEQ ID NO:102, 317, 211, 212	
TEM 10		TTTGGTTTTC C	TTTGGTTTTCCTCAAAA GA	J03464, M18057, X02488	SEQ ID NO:103, 319, 213, 214	Human collagen alpha-2 type I mRNA, complete cds, clone pHCOL2A1.
TEM 11		ATTTTGTATG A	ATTTTGTATGATTTT TA	NM_002508	SEQ ID NO:104, 321, 215, 216	nidogen/entactin
TEM 12		ACTTTAGATG G	ACTTTAGATGGGAA GCC	X52022	SEQ ID NO:105, 322, 217, 218	H.sapiens RNA for type VI collagen alpha3 chain.
TEM 13		GAGTGAGAC CC	GAGTGAGACCCAGG AGC	M11749	SEQ ID NO:106, 324, 219, 220	Human Thy-1 glycoprotein gene, complete cds.
TEM 14		GTACACACA CC	GTACACACACCCCC ACC		SEQ ID NO:107, 325, 221, 223	Cystatin SN

TEM 14	GTACACACA CC	GTACACACACCCCC ACC	X54667	SEQ ID NO:107, 325, 222, 224	H.sapiens mRNA for cystatin S.
TEM 15	CCACAGGGG AT	CCACAGGGGATTCT CCT	NM_00009 0	SEQ ID NO:108, 327, 225, 226	Human mRNA 3' region for pro-alpha 1(III) collagen.
TEM BSC- 16 TEM6	TTAAAAGTCA C	TTAAAAGTCACTGTG CA		SEQ ID NO:109, 328, 227, 228	
TEM BSC- 17 TEM7	ACAGACTGTT A	ACAGACTGTTAGCC AAG	AF279144	SEQ ID NO:110, 329, 229, 230	Human Tumor endothelial marker 7
TEM 18	CCACTGCAA CC			SEQ ID NO:111	
TEM BSC- 19 TEM8	CTATAGGAG AC			SEQ ID NO:112, 330, 231, 232	
TEM 20	GTTCCACAG AA		NM_00008 9	SEQ ID NO:113, 233, 234	collagen, type I, alpha 2 (COL1A2)

TEM 21	TACCACCTC CC	TACCACCTCCCCTTTC CT		SEQ ID NO:114, 331, 235, 236	Homo sapiens mRNA; cDNA DKFZp762B245 (from clone DKFZp762B245);
TEM 22	BSC- TEM9	GCCCTTTCTC T	NM_00603 9	SEQ ID NO:115, 334, 237, 238	endocytic receptor (macrophage mannose receptor family) (KIAA0709),
TEM 23		TTAAATAGCA C		SEQ ID NO:116, 335	no match
TEM 24		AGACATACT GA	NM_02264 8	SEQ ID NO:117, 336, 239, 240	Homo sapiens mRNA; cDNA DKFZp434G162 (from clone DKFZp434G162);
TEM 25		TCCCCCAGG AG	L35279, NM_00612 9	SEQ ID NO:118, 338, 241, 242	Homo sapiens (clone KT2) bone morphogenetic protein-1 (BMP-1) mRNA
TEM 26		AGCCCAAAG TG		SEQ ID NO:119	No Match
TEM 27		ACTACCATAA C	NM_00306 2	SEQ ID NO:120, 243,244	Homo sapiens mRNA for MEGF5, partial cds.
TEM 28		TACAAATCGT T	NM_01485 9	SEQ ID NO:121, 339, 245, 246	Homo sapiens mRNA for KIAA0672 protein, complete cds.

TEM 29	TTGGGTGAA AA				SEQ ID NO:122, 247, 248	ESTs (2 unigene clusters)
TEM 30	CATTATCCAA A	CATTATCCAAAACA AT	THC53402 9, X68742, AI262158, AI88747, AI394565, AA679721	SEQ ID NO:123, 340, 249, 250	integrin, alpha 1	
TEM 31	AGAAACCAC GG	AGAAACCACGGAAA TGG	NM_00184 5	SEQ ID NO:124, 341, 251, 252	hypothetical protein KIAA1164	
TEM 32	ACCAAACC AC			SEQ ID NO:125	no match	
TEM 33	TGAAATAAAC		NM_00025 5	SEQ ID NO:126, 253, 254	methylmalonyl Coenzyme A mutase	
TEM 34	TTTGGTTTCC			SEQ ID NO:127	no match	
TEM 35	GTGGAGACG GA	GTGGAGACGGACTC TGT	ESTAI186 535	SEQ ID NO:128, 345, 255, 358	est	

TEM 36	TTTGTGTTGT A	TTTGTGTTGTATATT TA	NM_00437 0	SEQ ID NO:129, 346, 256, 257	est
TEM 37	TTATGTTTAA T	TTATGTTTAATAGTT GA	NM_00234 5	SEQ ID NO:130, 347, 258, 259	Human lumican mRNA, complete cds.
TEM 38	TGGAATGA C	TGGAATGACCCAA AAA	NM_00008 8	SEQ ID NO:131, 348, 260, 261	collagen type1 alpha1
TEM 39	TGCCACACA GT	TGCCACACAGTGAC TTG	NM_00323 9	SEQ ID NO:132, 350, 262, 263	Human transforming growth factor-beta 3 (TGF-beta3) mRNA, complete
TEM 40	GATGAGGAG AC	GATGAGGAGACTGG CAA		SEQ ID NO:133, 351, 264, 265	collagen, type I, alpha 2
TEM 41	ATCAAAGGTT T	ATCAAAGGTTTGATT TA		SEQ ID NO:134, 352, 266, 267	est
TEM 42	AGTCACTAGT	AGTCACATAGTACAT AA	NM_02522 6	SEQ ID NO: 135, 353, 268, 269	ESTs

TEM 43	TTCGGTTGG TC	TTCGGTTGGTCAAA GAT		SEQ ID NO:136, 354	No match
TEM 44	CCCCACACG GG	CCCCACACGGGCAA GCA	NM_01835 4v	SEQ ID NO: 137, 355, 270, 271	Homo sapiens cDNA FLJ11190 fis, clone PLACE1007583.
TEM 45	GGCTTGCCT TT	GGCTTGCCTTTTGT AT	NM_00036 6	SEQ ID NO:138, 356, 272, 273	est
TEM 46	ATCCCTTCCC G	ATCCCTTCCCGCCA CAC	NM_00268 8	SEQ ID NO:139, 357, 274, 275	Homo sapiens mRNA for peanut-like protein 1, PNU1TL1 (hCDCrel-1).

- [53] The studies described below provide the first definitive molecular characterization of ECs in an unbiased and general manner. They lead to several important conclusions that have direct bearing on long-standing hypotheses about angiogenesis. First, it is clear that normal and tumor endothelium are highly related, sharing many endothelial cell specific markers. Second, it is equally clear that the endothelium derived from tumors is qualitatively different from that derived from normal tissues of the same type and is also different from primary endothelial cultures. Third, these genes are characteristically expressed in tumors derived from several different tissue types, documenting that tumor endothelium, in general, is different from normal endothelium. Fourth, the genes expressed differentially in tumor endothelium are also expressed during other angiogenic processes such as corpus luteum formation and wound healing. It is therefore more appropriate to regard the formation of new vessels in tumors as "neoangiogenesis" rather than "tumor angiogenesis" *per se*. This distinction is important from a variety of perspectives, and is consistent with the idea that tumors recruit vasculature using much of, or basically the same signals elaborated during other physiologic or pathological processes. That tumors represent "unhealed wounds" is one of the oldest ideas in cancer biology.
- [54] The nature and precise biological function of many of the Tumor Endothelial Markers (TEMs) identified here are unknown. Of the previously characterized genes shown in Table 2, it is intriguing that several encode proteins involved in extracellular matrix formation or remodelling (TEM 6, TEM 6, TEM 10, TEM 7, TEM 11, TEM 12, TEM 14, TEM 20, TEM 24, TEM 25, TEM 27, TEM 37, TEM 38, and TEM 40,) Deposition of extracellular matrix is likely critical to the growth of new vessels. Finally, it is perhaps not surprising that so many of the endothelial-specific transcripts identified here, whether expressed only in neovasculature or in endothelium in general, have not been previously characterized, and some are not even represented in EST databases. In part, this may be due to the fact that the EST databases are heavily biased toward certain

tissues, but moreover, may be due to the fact that even in highly vascularized tissues endothelial cells are still a relatively small proportion of the population. Thus, the sensitivity of the SAGE method is a particularly appropriate tool.

- [55] Sequence and literature study has permitted the following identifications to be made among the family of TEM proteins. TEM proteins have been identified which contain transmembrane regions. These include TEM 1, TEM 3, TEM 9, TEM 13, TEM 17, TEM 19, TEM 22, TEM 30, and TEM 44. TEM proteins have been identified which are secreted proteins, including TEM 4, TEM 6, TEM 7, TEM 10, TEM 12, TEM 14, TEM 20, TEM 25, TEM 27, TEM 31, TEM 36, TEM 37, TEM 38, and TEM 39. HeyL (TEM 8) is a transcription factor which may be involved in regulating TEMs as one or more groups. The protein corresponding to the tag for TEM44 was found in the public databases, but no biological function has yet been ascribed to it.
- [56] TEM 1 has been named endosialin in the literature. It has a signal sequence at amino acids 1-17 and a transmembrane domain at amino acids 686-708. Thus it is a cell surface protein. Its extracellular domain is at residues 1-685. Endosialin may be involved in endocytosis. The mouse ortholog is predicted to have a signal peptide at residues 1-21.
- [57] TEM 2 is a dexamethasone induced, ras related protein homolog of 266 amino acids. It has neither a signal sequence nor a transmembrane domain. Thus it is neither a cell surface nor a secreted protein. TEM 2 plays a role in signal transduction. It regulates alterations in cell morphology, proliferation, and cell-extracellular matrix interactions.
- [58] TEM 3 (originally termed TEM 7R) has both a signal sequence (at residues 1-24 or 1-30) and a transmembrane domain (at residues 456 – 477). Thus it is a cell surface protein. The portion of the protein which is extracellular is at amino acids 1- 455. TEM 3 has domains with homology to integrins, plexin,

and adhesion molecules. TEM 3 may regulate GTPases that control signal transduction pathways linking plasma membrane receptors to the actin cytoskeleton. In the mouse ortholog, the signal peptide is predicted to be residues 1-30.

[59] TEM 4 is also known as DKK -3. It has a signal sequence (residues 1-16), suggesting that it is a secreted protein. TEM 4 regulates *wnt* signaling, and it may be involved in vasculogenesis and *wnt*-dependent signaling for endothelial growth. TEM 4 is an inhibitor of Wnt oncogene and such inhibition can be determined by assay. Tsuji et al., *Biochem.Biophys.Res.Comm.* 268:20-4, 2000.

[60] TEM 5 appears to be neither secreted nor a cell surface protein. TEM 5 appears to be a component of a G protein - GTPase signaling pathway.

[61] TEM 6 is also known as stromelysin - 3 /Matrix metalloproteinase 11 (MMP -11). It has a signal sequence at residues 1-31, but no transmembrane domain. It has an alternative signal peptide splice site at residues 108-109. Thus it appears to be a secreted protein. TEM 6 belongs to the zinc metalloprotease family, also known as the *matrixin* subfamily. TEM 6 is expressed in most invasive carcinomas. Alpha 1 - protease inhibitor is a natural substrate of MMP 11. TEM 6 degrades extracellular matrix proteins such as collagen and is involved in extracellular matrix remodeling and cell migration. Stromelysin can be assayed using a casein-resorufin substrate, for example. See Tortorella and Arner, *Inflammation Research* 46 Supp. 2:S122-3, 1997.

[62] TEM 7 is a protein of many names, also being known as matrix metalloprotease 2, gelatinase A, and 72KD type IV collagenase. TEM 7 has a signal sequence at residues 1- 26 and is a secreted protein. Like TEM 6, TEM 7 belongs to the *matrixin* subfamily (zinc metalloproteinases). TEM 7 cleaves gelatin type I, collagen type I, IV, V VII and X.. TEM 7 associates with integrin on the surface of endothelial cells and promotes vascular invasion. TEM 7 is

involved in tissue remodeling. TEM 7 can be assayed using zymography or quenched fluorescent substrate hydrolysis, for example. Garbett, et al., *Molecular Pathology* 53:99-106, 2000. A fluorogenic matrix metalloproteinase substrate assay can also be used which employs methoxycoumarin containing septapeptide analog of the alpha2(I) collagen cleavage site. See Bhide et al., *J. Periodontology* 71:690-700, 2000.

[63] TEM 8 is HEYL protein. It has neither a signal sequence nor a transmembrane domain. It is related to the hairy/Enhancer of split genes. TEM 8 is likely a nuclear protein, having a role as a transcription factor. TEM 8 belongs to a new class of Notch signal transducers and plays a key role in various developmental processes, such as vascular development, somatogenesis and neurogenesis. SNP's at residues 615 and 2201 have Cytosine bases. Notch 3 mutations underlie the CADASIL vascular disorder. See *Mech Dev* 2000 Nov; 98 (1-2):175

[64] TEM 9 is a G-protein coupled receptor homolog, having both a signal sequence at residues 1-26 and 7 transmembrane domains. Thus it is a cell surface protein. Its extracellular region resides in amino acids 1-769. Its transmembrane domains are at residues 817-829 (TM2 and TM3), residues 899-929 (TM4 and TM5), and residues 1034-1040 (TM6 and TM7). TEM 9 acts as a G-protein coupled receptor with extracellular domains characteristic of cell adhesion proteins. One of its splice variants may function as a soluble receptor. TEM 9 may regulate cell polarity and cell migration. It may be involved in exocytosis based on latrophilin function. The mouse ortholog has a predicted signal peptide at residues 1-29.

[65] TEM 10 is collagen type I, alpha2 (COL1A2), which has a signal sequence at residues 1-22. It is an extracellular matrix (ECM) protein which is secreted subsequent to synthesis. TEM 10 interacts with a number of proteins including other ECM proteins, certain growth factors, and matrix metalloproteases. TEM

10 is required for the induction of endothelial tube formation and is involved in tissue remodeling. A variant at nucleotide 3233 which substitutes an A, is associated with osteogenesis imperfecta type IV. A variant at nucleotide 4321 substituting an A retains a wild type phenotype. Nucleotide 715 is a site of a polymorphism. Nucleotides 695-748 are deleted in Ehlers-Danos syndrome. Other mutations are associated with idiopathic osteoporosis, and atypical Marfan syndrome. Variants are known at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784 (G,C), 2017(T,G), 2172(C,A), 2284(T,C), 2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2974(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T). PolyA sites are located at nucleotides 4450, 4550, 4885, and 5082. PolyA signals are located at 4420-4424, 4515-4520, 4529-4534, 4866-4871, 5032-5037, 5053-5058. TEM 10, 20, and 40 derive from the same gene but are different isoforms having different lengths.

[66] TEM 11 is Nidogen /Entactin. It is a secreted protein which has a signal sequence at residues 1-28. TEM 11 is an extracellular matrix protein which is a component of a basement membrane. TEM 11 binds to laminin and collagen IV and other extracellular matrix proteins. TEM 11 regulates capillary formation and is involved in tissue remodelling. Variations have been observed at nucleotides 4265(T,C), 4267(G,C,T), and 4738(T,G). Nidogen can be assayed by its effect on the morphology of astrocytes. See Grimpe et al., GLIA 28:138-49, 1999.

[67] TEM 12 is the alpha 3 chain of collagen type VI. It has a signal sequence at residues 1-25. A secreted protein, TEM 12 is an extracellular matrix protein. TEM 12 has a splice variant. TEM 12 is a major constituent of vascular subendothelium and is involved in tissue remodeling. It regulates platelet activation and aggregation. Alternatively spliced domains are located at nucleotides 347-964, 965-1567, 2153-3752, and 4541-5041.

- [68] TEM 13 is also known as Thy -1 glycoprotein. It has both a signal sequence (at residues 1-19) and a transmembrane domain (at residues 143-159). Residues 131-161 are removed in a matured form of the protein. The extracellular region of the protein is residues 1- 142 or residues 1-130. TEM 13 has a glycosyl phosphatidylinositol (GPI) anchor at residue 130 anchoring it to the membrane. TEM 13 is detectable in its soluble form in human serum. TEM 13 is reported to be a marker for activated endothelial cells (a marker of adult but not embryonic angiogenesis). TEM 13 on vascular endothelial cells may function as a possible vascular permeability modulator. Antibody to Thy-1 is a mitogenic signal for the CD4+CD45+ and CD8+CD45+ cells, but fails to induce proliferation in the CD45- T cells. Pingel et al., *International Immunology* 6:169-78, 1994. Thy-1 can be assayed as an inhibitor of such signal.
- [69] TEM 14 is also known as cystatin S. It is a secreted protein with a signal sequence at residues 1-20 and an extracellular region at residues 1-141. It is a cysteine protease inhibitor. TEM 14 may regulate cysteine protease function involved in angiogenesis and tissue remodeling. TEM14 is an inhibitor of the activity of papain and such inhibition can be assayed. Hiltke et al., *J. Dental Research* 78:1401-9, 1999.
- [70] TEM 15 is collagen type III, alpha 1 (COL3A1). It has a signal sequence (residues 1-23) and is secreted. Type III collagen binds to von Willebrand factor. It is involved in cell-cell adhesion, proliferation, and migration activities. Variants at nucleotides 2104(C,A), 2194(G,A), 2346(C,T), 2740(C,T), 3157(T), 3468(G), 3652(T), 3666(C), 3693(C), 3755(G), 3756(T), 3824(C), 4546(A, G), 4661(G), 4591(C,T), 4665(C), 5292(C), 5293(C), and 5451 (A) have been observed.
- [71] TEM 16 is a tensin homolog which is apparently an intracellular protein. It may have splice variants or isoforms. One form with 1704 amino acids has a region at the N-terminal domain which is similar to a tumor suppressor protein,

phosphatase and tensin homolog (PTEN). Tensin is a focal adhesion molecule that binds to actins and phosphorylated proteins. It is involved in cell migration linking signal transduction pathways to the cytoskeleton. PTEN regulates tumor induced angiogenesis.

- [72] TEM 17 (BSC-TEM 7) has a signal sequence which includes residues 1-18 and a transmembrane domain at residues 427-445. It is a cell surface marker with an extracellular region comprising residues 1-426. It has homologs in both mouse and *C. elegans*. Residues 137-244 share weak homology with nidogen; residues 280-344 share homology to PSI domains found in plexin, semaphorins and integrin beta subunits. Variants have been observed at nucleotides 1893(A,G), 1950(C,G), 2042(A,G), and 2220(G,A). In mouse TEM 17 the signal sequence includes residues 1-19.
- [73] TEM 19 was originally reported to be tumor endothelial marker 8, *i.e.*, BSC-TEM 8. It has a signal sequence at residues 1-27 and a transmembrane domain at residues 322-343. It is a cell surface protein having an extracellular region at residues 1-321. TEM 19 has a von Willebrand Factor (vWF) A domain at residues 44-216; a domain at residues 34-253 which is found in leukointegrin alpha D chain; and a domain at residues 408-560 found in PRAM-1 or adaptor molecule -1 of the vinculin family. TEM 19's function is adhesion related. vonWillebrand Factor domains are typically involved in a variety of functions including vascular processes. TEM 19 may play a role in the migration of vascular endothelial cells. The mouse ortholog has a predicted signal peptide at residues 1-27.
- [74] TEM 20 is collagen type I, alpha 2 (COL1A2). It has a signal sequence at residues 1-22 and is a secreted extracellular matrix protein. TEM 20 induces endothelial tube formation *in vitro* and is involved in tissue remodeling. Variants have been observed at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784(G,C), 2017(T,G), 2172(C,A), 2284(T,C),

2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2794(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4895-4901(--, GGACAAC), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T).

[75] TEM 21 is a Formin – like protein homolog which is an intracellular protein. Formin related proteins interact with Rho family small GTPases, profilin, and other actin associated proteins. Formin-binding proteins bind to FH1 domains with their WW domains. TEM 21 has a proline rich FH1 domain at residues 221-449. Formin related proteins play crucial roles in morphogenesis, cell polarity, cytokinesis and reorganization of the actin cytoskeleton. They may also regulate apoptosis, cell adhesion and migration.

[76] TEM 22 is an endocytic receptor in the macrophage mannose receptor family. It has both a signal sequence at residues 1-30 and a transmembrane domain at residues 1415-1435, and resides on the cell surface. Its extracellular domain is amino acids 1- 1414. TEM 22 may be present as a soluble (secreted) form and act as an inhibitor. It may bind secreted phospholipase A2 (sPLA2) and mediate biological responses elicited by sPLA2. TEM 22 may have endocytic properties for sPLA2 and mediate endocytosis for endothelial related proteins. It may promote cell adhesion and be involved in cell-cell communication. Variations have been observed at nucleotide 5389 (A, G). TEM 22 mediates uptake of micro-organisms and host-derived glycoproteins. Groger et al., J. Immunology 165:5428-34, 2000.

[77] TEM 24 is tensin, an intracellular protein. It is a focal adhesion molecule that binds to actin filaments and interacts with phosphotyrosine containing proteins. It may mediate kinase signaling activities and regulate cellular transformation. Variations have been observed at nucleotides 2502 (A, G), 2622(A, G), 6027(A, G). TEM24 binds to actin filaments and interacts with phosphotyrosine-containing proteins. Chen et al., Biochem. J. 351 Pt2:403-11,

2000. TEM24 also binds to phosphoinositide3-kinase. Auger et al., J. Bio. Chem. 271:23452-7, 1996 TEM 24 also binds to nuclear protein p130. Lo et al., Bioessays 16:817-23, 1994.

[78] TEM 25 is Bone morphogenic protein 1 (BMP-1) which has a signal sequence at residues 1-22. It is a secreted protein. There are at least 6 isoforms of BMP-1 as well as splice variants which add carboxy terminal CUB domains and an additional EGF domain. TEM 25 is a metalloprotease enzyme. It cleaves the C-terminal propeptide of collagen type I, II and III and laminin 5 gamma 2 , proteins that are important for vascular processes. It is involved in cartilage formation. Variations have been observed at nucleotides 3106(C,T), 3248(G,A), 3369(G,A). TEM 25 cleave probiglycan at a single site, removing the propeptide and producing a biglycan molecule with an NH(2) terminus identical to that of the mature form found in tissues. Scft et al., J. Biol. Chem. 275:30504-11, 2000. Laminin alpha 3 and gamma2 short chains are substraates of TEM 25. Amano et al., J. Biol. Chem. 275:22728-35, 2000.

[79] TEM 27 is known as Slit homolog 3, a secreted protein with a signal sequence at residues 1-27. TEM 27 is a secreted guide protein involved in migration, repulsion and patterning. It interacts with "round about" receptors (Robo receptors). TEM 27 may interact with extracellular matrix (ECM) proteins and is involved in cell adhesion. Variations have been observed at nucleotides 4772 (C,T)

[80] TEM 28 is similar to mouse nadrin (neuron specific GTPase activiating protein). TEM 28 is an intracellular protein with a RhoGAP domain. The RhoGAP domain activates RhoA, Rac1, and Cdc42 GTPases. It is involved in the reorganization of actin filaments and enhancing exocytosis. It may also be involved in cell signalling. Variations have been observed at nucleotide 3969 (A,C),

- [81] TEM 29 is protein tyrosine phosphatase type IVA, member 3, isoform 1, an intracellular protein. It has alternate splice variants. TEM 29 belongs to a small class of prenylated protein tyrosine phosphatases (PTPs). It may be membrane associated by prenylation. PTPs are cell signaling molecules and play regulatory roles in a variety of cellular processes and promote cell proliferation. PTP PRL-3 regulates angiotensin -II induced signaling events.
- [82] TEM 30 is integrin alpha 1, a cell surface protein having both a signal sequence (residues 1-28) and a transmembrane domain (residues 1142-1164). Its extracellular region includes amino acids 1-1141. TEM 30 is a receptor for laminin and collagen. It mediates a variety of adhesive interactions. TEM 30 is abundantly expressed on microvascular endothelial cells. It stimulates endothelial cell proliferation and vascularization. TEM 30 may regulate angiostatin production. Variations have been observed at nucleotide 418 (C,T). TEM 30 activates the Ras/Shc/mitogen-activated protein kinase pathway promoting fibroblast cell proliferation. It also acts to inhibit collagen and metalloproteinase synthesis. Pozzi et al., Proc. Nat. Acad. Sci. USA 97:2202-7, 2000,
- [83] TEM 31 is Collagen IV alpha 1 (COL4A1) a secreted protein with a at residues 1-27. TEM 31 is a component of the basement membrane. It binds to alpha3 beta 1 integrin and promotes integrin mediated cell adhesion. Non-collagenous domains of type IV subunits are involved in tumoral angiogenesis. TEM 31 is involved in tissue remodeling. Variations have been observed at nucleotide 4470 (C,T)
- [84] TEM 33 is methylmalonyl Co-A Mutase a protein which is localized in the mitochondrial matrix. It degrades several amino acids, odd-numbered-acid fatty acids, and cholesterol to the tricarboylic acid cycle. A defect in TEM 33 causes a fatal disorder in organic acid metabolism termed methylmalonic acidurea. Variations have been observed at nucleotides 1531(G,A), 1671(G,A), 2028(T,C), 2087(G,A), 2359(A,G), 2437(C,A), 2643(G,C), 2702(G,C). TEM 33

converts L-methylmalonyl CoA to succinyl CoA. This reaction can be assayed as is known in the art. See, e.g., Clin. Chem. 41(8 Pt 1):1164-70, 1995.

- [85] TEM 36 is collagen type XII, alpha1 (COL12A1), an extracellular matrix protein having a signal sequence at residues 1-23 or 24. TEM 36 has von Willebrand Factor (vWF) type A domains, Fibronectin type III domains, and thrombospondin N-terminal like domain. TEM 36 is expressed in response to stress environment. TEM 36 may organize extracellular matrix architecture and be involved in matrix remodeling. There are two isoforms of the protein, a long form and a short form. The short form is missing amino acids 25-1188, and therefore nucleotides 73 to 3564. Both forms share the signal sequence and are therefore both secreted.
- [86] TEM 37 is lumican, an extracellular matrix sulfated proteoglycan having a signal sequence at residues 1-18. Lumican interacts with proteins that are involved in matrix assembly such as collagen type I and type VI; it is involved in cell proliferation and tissue morphogenesis. Lumican plays an important role in the regulation of collagen fiber assembly. Variations have been observed at nucleotides 1021(G,T), 1035(A,G), 1209(A,G), 1259(A,C), 1418(C,A), 1519(T,A). TEM 37 is a binding partner of TGF- β . See FASEB J. 15:559-61, 2000. One assay that can be used to determine TEM 37 activity is a collagen fibril formation/sedimentation assay. Svensson et al., FEBS Letters 470:178-82, 2000.
- [87] TEM 38 is collagen type I, alpha 1 (COL1A1), an extracellular matrix protein having a signal sequence at residues 1-22. Type I collagen promotes endothelial cell migration and vascularization and induces tube formation and is involved in tissue remodelling. Telopeptide derivative is used as a marker for malignancy and invasion for certain cancer types. Variations have been observed at nucleotides 296(T,G), 1810(G,A), 1890(G,A), 2204(T,A), 3175(G,C), 3578(C,T), 4298(C,T), 4394(A,T), 4410(A,C), 4415(C,A), 4419 (A,T), 4528(C,A), 4572(G,T), 4602(T,C), 5529(T,C), 5670(C,T), 5985(C,T), 6012(C,T).

- [88] TEM 39 is transforming growth factor β -3 (TGF-beta3). It has a signal sequence at residues 1-23. It is a secreted protein. TEM 39 regulates cell growth and differentiation. TGF-beta isoforms play a major role in vascular repair processes and remodeling. Variations have been observed at nucleotide 2020(G,T).
- [89] TEM 41 is similar to Olfactomedin like protein. It appears to be an intracellular protein, having no obvious predicted signal sequence. Olfactomedin is the major glycoprotein of the extracellular mucous matrix of olfactory neuroepithelium. TEM 41 shares homology with latrophilin (extracellular regions) which has cell-adhesive type domains. TEM 41 may be involved in adhesive function.
- [90] TEM 42 is MSTP032 protein, a cell surface protein having a transmembrane domain at residues 42-61. Its function is unknown and it shares little homology with other proteins. Variations have been observed at nucleotides 418(A,T), 724(C,A).
- [91] TEM 44 is a hypothetical protein FLJ11190 (NM_018354) which has two predicted transmembrane domains at residues 121-143 and 176-197. Residues 144-175 may form an extracellular region. TEM 44's function is not known and shares no homology to other known proteins.
- [92] TEM 45 is tropomyosin 1 (alpha), a protein which is intracellular. It forms dimers with a beta subunit. It influences actin function. TEM 45 may be involved in endothelial cell cytoskeletal rearrangement. Variations have been observed at nucleotides 509(A,C), 621(A,C), 635(T,G), 642(C,G), 1059(G,T).
- [93] TEM 46 is peanut-like 1 protein/septin 5, which belongs to the septin family. Proteins in the septin family bind to GTP and phosphatidylinositol 4,5-bisphosphate. They are involved in the signal transduction cascades controlling cytokinesis and cell division.

- [94] NEM 4 is a member of the small inducible cytokine subfamily A (cys-cys), member 14 (SCYA14). NEM4 is a secreted protein characterized by two adjacent cysteine residues. One isoform lacks internal 16 amino acids compared to isoform 2.
- [95] NEM 22 shares homology with guanylate kinase-interacting protein 1Maguin-1. It is a membrane associated protein.
- [96] NEM 23 is human signaling lymphocytic activation molecule (SLAM). It has a signal sequence at residues 1-20. The extracellular domain may reside at residues 21-237. There is a secreted isoform of the protein.
- [97] NEM33 is netrin 4. It induces neurite outgrowth and promotes vascular development. At higher concentration, neurite outgrowth is inhibited.
- [98] ECs represent only a minor fraction of the total cells within normal or tumor tissues, and only those EC transcripts expressed at the highest levels would be expected to be represented in libraries constructed from unfractionated tissues. The genes described in the current study should therefore provide a valuable resource for basic and clinical studies of human angiogenesis in the future. Genes which have been identified as tumor endothelial markers (TEMs) correspond to tags shown in SEQ ID NOS: 94-139, 173-176, 180-186. Genes which have been identified as normal endothelial markers (NEMs) correspond to tags shown in SEQ ID NOS: 140-172. Genes which have been identified as pan-endothelial markers (PEMs) *i.e.*, expressed in both tumor and normal endothelial cells correspond to tags shown in SEQ ID NOS: 1-93. Genes which have been previously identified as being expressed predominantly in the endothelium correspond to PEM tags shown in SEQ ID NOS: 1-6, 8, 10-15. Markers in each class can be used interchangeably for some purposes.

[99] Isolated and purified nucleic acids, according to the present invention are those which are not linked to those genes to which they are linked in the human genome. Moreover, they are not present in a mixture such as a library containing a multitude of distinct sequences from distinct genes. They may be, however, linked to other genes such as vector sequences or sequences of other genes to which they are not naturally adjacent. Tags disclosed herein, because of the way that they were made, represent sequences which are 3' of the 3' most restriction enzyme recognition site for the tagging enzyme used to generate the SAGE tags. In this case, the tags are 3' of the most 3' most NlaIII site in the cDNA molecules corresponding to mRNA. Nucleic acids corresponding to tags may be RNA, cDNA, or genomic DNA, for example. Such corresponding nucleic acids can be determined by comparison to sequence databases to determine sequence identities. Sequence comparisons can be done using any available technique, such as BLAST, available from the National Library of Medicine, National Center for Biotechnology Information. Tags can also be used as hybridization probes to libraries of genomic or cDNA to identify the genes from which they derive. Thus, using sequence comparisons or cloning, or combinations of these methods, one skilled in the art can obtain full-length nucleic acid sequences. Genes corresponding to tags will contain the sequence of the tag at the 3' end of the coding sequence or of the 3' untranslated region (UTR), 3' of the 3' most recognition site in the cDNA for the restriction endonuclease which was used to make the tags. The nucleic acids may represent either the sense or the anti-sense strand. Nucleic acids and proteins although disclosed herein with sequence particularity, may be derived from a single individual. Allelic variants which occur in the population of humans are including within the scope of such nucleic acids and proteins. Those of skill in the art are well able to identify allelic variants as being the same gene or protein. Given a nucleic acid, one of ordinary skill in the art can readily determine an open reading frame present, and consequently the sequence of a polypeptide encoded by the open reading frame and, using techniques well known in the art, express such protein in a suitable

host. Proteins comprising such polypeptides can be the naturally occurring proteins, fusion proteins comprising exogenous sequences from other genes from humans or other species, epitope tagged polypeptides, etc. Isolated and purified proteins are not in a cell, and are separated from the normal cellular constituents, such as nucleic acids, lipids, etc. Typically the protein is purified to such an extent that it comprises the predominant species of protein in the composition, such as greater than 50, 60 70, 80, 90, or even 95% of the proteins present.

[100] Using the proteins according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[101] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p.

1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods* 231 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D, Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy. *Cancer Research* Vol. 59, Number 6, pp1236-1243 (1999) ; Jakobovits A. Production and selection of antigen-specific fully human monoclonal antibodies from mice engineered with human Ig loci. *Advanced Drug Delivery Reviews* Vol. 31, pp: 33-42 (1998); Green L and Jakobovits A. Regulation of B cell development by variable gene complexity in mice reconstituted with human immunoglobulin yeast artificial chromosomes. *J. Exp. Med.* Vol. 188, Number 3, pp: 483-495 (1998); Jakobovits A. The long-awaited magic bullets: therapeutic human monoclonal antibodies from transgenic mice. *Exp. Opin. Invest. Drugs* Vol. 7(4), pp : 607-614 (1998) ; Tsuda H, Maynard-Currie K, Reid L, Yoshida T, Edamura K, Maeda N, Smithies O, Jakobovits A. Inactivation of Mouse HPRT locus by a 203-bp retrotransposon insertion and a 55-kb gene-targeted deletion: establishment of new HPRT-Deficient mouse embryonic stem cell lines. *Genomics* Vol. 42, pp: 413-421 (1997) ; Sherman-Gold, R. Monoclonal Antibodies: The Evolution from '80s Magic Bullets To Mature, Mainstream Applications as Clinical Therapeutics. *Genetic Engineering News* Vol. 17, Number 14 (August 1997); Mendez M, Green L, Corvalan J, Jia X-C, Maynard-Currie C, Yang X-d, Gallo M, Louie D, Lee D, Erickson K, Luna J, Roy C, Abderrahim H, Kirschenbaum F, Noguchi M,

Smith D, Fukushima A, Hales J, Finer M, Davis C, Zsebo K, Jakobovits A. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nature Genetics* Vol. 15, pp: 146-156 (1997); Jakobovits A. Mice engineered with human immunoglobulin YACs: A new technology for production of fully human antibodies for autoimmunity therapy. *Weir's Handbook of Experimental Immunology, The Integrated Immune System* Vol. IV, pp: 194.1-194.7 (1996) ; Jakobovits A. Production of fully human antibodies by transgenic mice. *Current Opinion in Biotechnology* Vol. 6, No. 5, pp: 561-566 (1995) ; Mendez M, Abderrahim H, Noguchi M, David N, Hardy M, Green L, Tsuda H, Yoast S, Maynard-Currie C, Garza D, Gemmill R, Jakobovits A, Klapholz S. Analysis of the structural integrity of YACs comprising human immunoglobulin genes in yeast and in embryonic stem cells. *Genomics* Vol. 26, pp: 294-307 (1995); Jakobovits A. YAC Vectors: Humanizing the mouse genome. *Current Biology* Vol. 4, No. 8, pp: 761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al., U.S. 6,1075,181.

[102] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[103] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample. Antibodies can also be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis Factor (TNF); photosensitizers, for use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m ($^{99\text{m}}\text{Tc}$), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (*naja naja atra*), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*,

antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

- [104] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.
- [105] Characterization of extracellular regions for the cell surface and secreted proteins from the protein sequence is based on the prediction of signal sequence, transmembrane domains and functional domains. Antibodies are preferably specifically immunoreactive with membrane associated proteins, particularly to extracellular domains of such proteins or to secreted proteins. Such targets are readily accessible to antibodies, which typically do not have access to the interior of cells or nuclei. However, in some applications, antibodies directed to intracellular proteins may be useful as well. Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay.
- [106] Computer programs can be used to identify extracellular domains of proteins whose sequences are known. Such programs include SMART software (Schultz et al., Proc. Natl. Acad. Sci. USA 95: 5857-5864, 1998) and Pfam software (Bateman et al., Nucleic acids Res. 28: 263-266, 2000) as well as PSORTIL. Typically such programs identify transmembrane domains; the extracellular domains are identified as immediately adjacent to the transmembrane domains. Prediction of extracellular regions and the signal cleavage sites are only approximate. It may have a margin of error + or - 5 residues. Signal sequence can be predicted using three different methods (Nielsen et al, *Protein Engineering* 10: 1-6, 1997, Jagla et. al, *Bioinformatics* 16: 245-250, 2000, Nakai, K and Horton, P. *Trends in Biochem. Sci.* 24:34-35, 1999) for greater accuracy.

Similarly transmembrane (TM) domains can be identified by multiple prediction methods. (Pasquier, et. al, Protein Eng. 12:381-385, 1999, Sonnhammer et al., In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p. 175-182 , Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, CA: AAAI Press, 1998 , Klein, et.al, Biochim. Biophys. Acta, 815:468, 1985, Nakai and Kanehisa Genomics, 14: 897-911 , 1992). In ambiguous cases, locations of functional domains in well characterized proteins are used as a guide to assign a cellular localization.

[107] Putative functions or functional domains of novel proteins can be inferred from homologous regions in the database identified by BLAST searches (Altschul et. al. Nucleic Acid Res. 25: 3389-3402, 1997) and/or from a conserved domain database such as Pfam (Bateman et.al, Nucleic Acids Res. 27:260-262 1999) BLOCKS (Henikoff, et. al, Nucl. Acids Res. 28:228-230, 2000) and SMART (Ponting, et. al, Nucleic Acid Res. 27,229-232, 1999). Extracellular domains include regions adjacent to a transmembrane domain in a single transmembrane domain protein (out-in or type I class). For multiple transmembrane domains proteins, the extracellular domain also includes those regions between two adjacent transmembrane domains (in-out and out-in). For type II transmembrane domain proteins, for which the N-terminal region is cytoplasmic, regions following the transmembrane domain is generally extracellular. Secreted proteins on the other hand do not have a transmembrane domain and hence the whole protein is considered as extracellular.

[108] Membrane associated proteins can be engineered to delete the transmembrane domains, thus leaving the extracellular portions which can bind to ligands. Such soluble forms of transmembrane receptor proteins can be used to compete with natural forms for binding to ligand. Thus such soluble forms act as inhibitors. and can be used therapeutically as anti-angiogenic agents, as diagnostic tools for the quantification of natural ligands, and in assays for the identification of small molecules which modulate or mimic the activity of a TEM:ligand complex.

[109] Alternatively, the endothelial markers themselves can be used as vaccines to raise an immune response in the vaccinated animal or human. For such uses, a protein, or immunogenic fragment of such protein, corresponding to the intracellular, extracellular or secreted TEM of interest is administered to a subject. The immunogenic agent may be provided as a purified preparation or in an appropriately expressing cell. The administration may be direct, by the delivery of the immunogenic agent to the subject, or indirect, through the delivery of a nucleic acid encoding the immunogenic agent under conditions resulting in the expression of the immunogenic agent of interest in the subject. The TEM of interest may be delivered in an expressing cell, such as a purified population of tumor endothelial cells or a populations of fused tumor endothelial and dendritic cells. Nucleic acids encoding the TEM of interest may be delivered in a viral or non-viral delivery vector or vehicle. Non-human sequences encoding the human TEM of interest or other mammalian homolog can be used to induce the desired immunologic response in a human subject. For several of the TEMs of the present invention, mouse, rat or other ortholog sequences are described herein or can be obtained from the literature or using techniques well within the skill of the art.

[110] Endothelial cells can be identified using the markers which are disclosed herein as being endothelial cell specific. These include the human markers identified by SEQ ID NOS: 1-172, *i.e.*, the normal, pan-endothelial, and the tumor endothelial markers. Homologous mouse markers include tumor endothelial markers of SEQ ID NO: 182-186 and 190-194. Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells. The presence of cross-reactive material with the antibodies identifies particular cells as endothelial. Similarly, lysates of cells can be tested for the presence of cross-reactive material. Any known format or technique for detecting cross-reactive material can be used including, immunoblots, radioimmunoassay, ELISA, immunoprecipitation, and

immunohistochemistry. In addition, nucleic acid probes for these markers can also be used to identify endothelial cells. Any hybridization technique known in the art including Northern blotting, RT-PCR, microarray hybridization, and in situ hybridization can be used.

- [111] One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more TEMs. One can test both tissues and bodily fluids of a subject. For example, one can test a patient's blood for evidence of intracellular and membrane associated TEMs, as well as for secreted TEMs. Intracellular and/or membrane associated TEMs may be present in bodily fluids as the result of high levels of expression of these factors and/or through lysis of cells expressing the TEMs.
- [112] Populations of various types of endothelial cells can also be made using the antibodies to endothelial markers of the invention. The antibodies can be used to purify cell populations according to any technique known in the art, including but not limited to fluorescence activated cell sorting. Such techniques permit the isolation of populations which are at least 50, 60, 70, 80, 90, 92, 94, 95, 96, 97, 98, and even 99 % the type of endothelial cell desired, whether normal, tumor, or pan-endothelial. Antibodies can be used to both positively select and negatively select such populations. Preferably at least 1, 5, 10, 15, 20, or 25 of the appropriate markers are expressed by the endothelial cell population.
- [113] Populations of endothelial cells made as described herein, can be used for screening drugs to identify those suitable for inhibiting the growth of tumors by virtue of inhibiting the growth of the tumor vasculature.
- [114] Populations of endothelial cells made as described herein, can be used for screening candidate drugs to identify those suitable for modulating angiogenesis, such as for inhibiting the growth of tumors by virtue of inhibiting the growth of endothelial cells, such as inhibiting the growth of the tumor or other undesired

vasculature, or alternatively, to promote the growth of endothelial cells and thus stimulate the growth of new or additional large vessel or microvasculature.

[115] Inhibiting the growth of endothelial cells means either regression of vasculature which is already present, or the slowing or the absence of the development of new vascularization in a treated system as compared with a control system. By stimulating the growth of endothelial cells, one can influence development of new (neovascularization) or additional vasculature development (revascularization). A variety of model screen systems are available in which to test the angiogenic and/or anti-angiogenic properties of a given candidate drug. Typical tests involve assays measuring the endothelial cell response, such as proliferation, migration, differentiation and/or intracellular interaction of a given candidate drug. By such tests, one can study the signals and effects of the test stimuli. Some common screens involve measurement of the inhibition of heparanase, endothelial tube formation on Matrigel, scratch induced motility of endothelial cells, platelet-derived growth factor driven proliferation of vascular smooth muscle cells, and the rat aortic ring assay (which provides an advantage of capillary formation rather than just one cell type).

[116] Drugs can be screened for the ability to mimic or modulate, inhibit or stimulate, growth of tumor endothelium cells and/or normal endothelial cells. Drugs can be screened for the ability to inhibit tumor endothelium growth but not normal endothelium growth or survival. Similarly, human cell populations, such as normal endothelium populations or tumor endothelial cell populations, can be contacted with test substances and the expression of tumor endothelial markers and/or normal endothelial markers determined. Test substances which decrease the expression of tumor endothelial markers (TEMs) are candidates for inhibiting angiogenesis and the growth of tumors. Conversely, markers which are only expressed in normal endothelium but not in tumor endothelium (NEMs) can be monitored. Test substances which increase the expression of such NEMs in tumor endothelium and other human cells can be identified as candidate antitumor or

anti-angiogenic drugs In cases where the activity of a TEM or NEM is known, agents can be screened for their ability to decrease or increase the activity.

[117] For those tumor endothelial markers identified as containing transmembrane regions, it is desirable to identify drug candidates capable of binding to the TEM receptors found at the cell surface. For some applications, the identification of drug candidates capable of blocking the TEM receptor from its native ligand will be desired. For some applications, the identification of a drug candidate capable of binding to the TEM receptor may be used as a means to deliver a therapeutic or diagnostic agent. For other applications, the identification of drug candidates capable of mimicing the activity of the native ligand will be desired. Thus, by manipulating the binding of a transmembrane TEM receptor:ligand complex, one may be able to promote or inhibit further development of endothelial cells and hence, vascularization.

[118] For those tumor endothelial markers identified as being secreted proteins, it is desirable to identify drug candidates capable of binding to the secreted TEM protein. For some applications, the identification of drug candidates capable of interfering with the binding of the secreted TEM to its native receptor. For other applications, the identification of drug candidates capable of mimicing the activity of the native receptor will be desired. Thus, by manipulating the binding of the secreted TEM:receptor complex, one may be able to promote or inhibit further development of endothelial cells, and hence, vascularization.

[119] Expression can be monitored according to any convenient method. Protein or mRNA can be monitored. Any technique known in the art for monitoring specific genes' expression can be used, including but not limited to ELISAs, SAGE, microarray hybridization, Western blots. Changes in expression of a single marker may be used as a criterion for significant effect as a potential pro-angiogenic, anti-angiogenic or anti-tumor agent. However, it also may be desirable to screen for test substances which are able to modulate the expression

of at least 5, 10, 15, or 20 of the relevant markers, such as the tumor or normal endothelial markers. Inhibition of TEM protein activity can also be used as a drug screen. Human and mouse TEMS can be used for this purpose.

[120] Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions which may previously have been overlooked in other screening schemes. Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. NEMs, can be used to restrict, diminish, reduce, or inhibit proliferation of tumor or other abnormal or undesirable vasculature. TEMs can be used to stimulate the growth of vasculature, such as for wound healing or to circumvent a blocked vessel. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include adenovirus, retroviruses, and sindbis virus. Administration modes can be any known in the art, including parenteral, intravenous, intramuscular, intraperitoneal, topical, intranasal, intrarectal, intrabronchial, etc.

[121] Specific biological antagonists of TEMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for a TEM, antisense to a TEM, and ribozymes specific for a TEM can be used to restrict, inhibit, reduce, and/or diminish tumor or other abnormal or undesirable vasculature growth. Such antagonists can be administered as is known in the art for these classes of antagonists generally. Anti-angiogenic drugs and agents can be used to inhibit tumor growth, as well as to treat diabetic retinopathy, rheumatoid arthritis, psoriasis, polycystic kidney disease (PKD), and other diseases requiring angiogenesis for their pathologies.

[122] Mouse counterparts to human TEMS can be used in mouse cancer models or in cell lines or *in vitro* to evaluate potential anti-angiogenic or anti-tumor compounds or therapies. Their expression can be monitored as an indication of effect. Mouse TEMs are disclosed in SEQ ID NO: 182-186 and 190-194. Mouse TEMs can be used as antigens for raising antibodies which can be tested in mouse tumor models. Mouse TEMs with transmembrane domains are particularly preferred for this purpose. Mouse TEMs can also be used as vaccines to raise an immunological response in a human to the human ortholog.

[123] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

Visualization of vasculature of colorectal cancers

[124] The endothelium of human colorectal cancer was chosen to address the issues of tumor angiogenesis, based on the high incidence, relatively slow growth, and resistance to anti-neoplastic agents of these cancers. While certain less common tumor types, such as glioblastomas, are highly vascularized and are regarded as good targets for anti-angiogenic therapy, the importance of angiogenesis for the growth of human colorectal cancers and other common solid tumor types is less well documented.

[125] We began by staining vessels in colorectal cancers using von Willebrand Factor (vWF) as a marker. In each of 6 colorectal tumors, this examination revealed a high density of vessels throughout the tumor parenchyma (Examples in Fig. 1 A and B). Interestingly, these analyses also substantiated the importance of these

vessels for tumor growth, as endothelium was often surrounded by a perivascular cuff of viable cells, with a ring of necrotic cells evident at the periphery (Example in Fig. 1A). Although these preliminary studies suggested that colon tumors are angiogenesis-dependent, reliable markers that could distinguish vessels in colon cancers from the vessels in normal colon are currently lacking. One way to determine if such markers exist is by analyzing gene expression profiles in endothelium derived from normal and neoplastic tissue.

EXAMPLE 2

Purification of endothelial cells

[126] Global systematic analysis of gene expression in tumor and normal endothelium has been hampered by at least three experimental obstacles. First, endothelium is enmeshed in a complex tissue consisting of vessel wall components, stromal cells, and neoplastic cells, requiring highly selective means of purifying ECs for analysis. Second, techniques for defining global gene expression profiles were not available until recently. And third, only a small fraction of the cells within a tumor are endothelial, mandating the development of methods that are suitable for the analysis of global expression profiles from relatively few cells.

[127] To overcome the first obstacle, we initially attempted to purify ECs from dispersed human colorectal tissue using CD31, an endothelial marker commonly used for this purpose. This resulted in a substantial enrichment of ECs but also resulted in contamination of the preparations by hematopoietic cells, most likely due to expression of CD31 by macrophages. We therefore developed a new method for purifying ECs from human tissues using P1H12, a recently described marker for ECs. Unlike CD31, P1H12 was specifically expressed on the ECs of both colorectal tumors and normal colorectal mucosa. Moreover, immunofluorescence staining of normal and cancerous colon with a panel of known cell surface endothelial markers (e.g. VE-cadherin, CD31 and CD34)

revealed that P1H12 was unique in that it stained all vessels including microvessels (see Fig. 2A and data not shown). In addition to selection with P1H12, it was necessary to optimize the detachment of ECs from their neighbors without destroying their cell surface proteins as well as to employ positive and negative affinity purifications using a cocktail of antibodies (Fig. 2B). The ECs purified from normal colorectal mucosa and colorectal cancers were essentially free of epithelial and hematopoietic cells as judged by RT-PCR (Fig. 2C) and subsequent gene expression analysis (see below).

EXAMPLE 3

Comparison of tumor and normal endothelial cell expression patterns

[128] To overcome the remaining obstacles, a modification of the Serial Analysis of Gene Expression (SAGE) technique was used. SAGE associates individual mRNA transcripts with 14 base pair tags derived from a specific position near their 3' termini. The abundance of each tag provides a quantitative measure of the transcript level present within the mRNA population studied. SAGE is not dependent on pre-existing databases of expressed genes, and therefore provides an unbiased view of gene expression profiles. This feature is particularly important in the analysis of cells that constitute only a small fraction of the tissue under study, as transcripts from these cells are unlikely to be well represented in extant EST databases. We adapted the SAGE protocol so that it could be used on small numbers of purified ECs obtained from the procedure outlined in Fig. 2B. A library of ~100,000 tags from the purified ECs of a colorectal cancer, and a similar library from the ECs of normal colonic mucosa from the same patient were generated. These ~193,000 tags corresponded to over 32,500 unique transcripts. Examination of the expression pattern of hematopoietic, epithelial and endothelial markers confirmed the purity of the preparations (Fig. 2D).

EXAMPLE 4

Markers of normal and tumor endothelium

[129] We next sought to identify Pan Endothelial Markers (PEMs), that is, transcripts that were expressed at significantly higher levels in both normal and tumor associated endothelium compared to other tissues. To identify such PEMs, tags expressed at similar levels in both tumor and normal ECs were compared to ~ 1.8 million tags from a variety of cell lines derived from tumors of non-endothelial origin. This simple comparison identified 93 transcripts that were strikingly EC-specific, i.e. expressed at levels at least 20-fold higher in ECs in vivo compared to non-endothelial cells in culture. The 15 tags corresponding to characterized genes which were most highly and specifically expressed in endothelium are shown in Table 1A. Twelve of these 15 most abundant endothelial transcripts had been previously shown to be preferentially expressed in endothelium, while the other 3 genes had not been associated with endothelium in the past (Table 1A). These data sets also revealed many novel PEMs, which became increasingly prevalent as tag expression levels decreased (Table 1B). For many of the transcripts, their endothelial origin was confirmed by SAGE analysis of ~401,000 transcripts derived from primary cultures of human umbilical vein endothelial cells (HUVEC) and human dermal microvascular endothelial cells (HMVEC) (Table 1 A and B). To further validate the expression of these PEMs in vivo, we developed a highly sensitive non-radioactive in situ hybridization method that allowed the detection of transcripts expressed at relatively low levels in frozen sections of human tissues. Two uncharacterized markers, PEM3 and PEM6, were chosen for this analysis. In each case, highly specific expression was clearly limited to vascular ECs in both normal and neoplastic tissues (Fig. 3 A and B and data not shown). These data also suggest that ECs maintained in culture do not completely recapitulate expression patterns observed in vivo. For example, Hevin and several other PEM's were expressed at high levels in both tumor and normal

ECs in vivo, but few or no transcripts were detected in cultured HUVEC or HMVEC (Table 1). The source of the Hevin transcripts was confirmed to be endothelium by in situ hybridization in normal and malignant colorectal tissue (Fig. 3C).

- [130] Many of the markers reported in Table 1 were expressed at significantly higher levels than previously characterized genes commonly associated with ECs. For example, the top 25 markers were all expressed at greater than 200 copies per cell. In contrast, the receptors for VEGF (VEGFR-1 and VEGFR-2) were expressed at less than 20 copies per cell. Interestingly, VEGFR2 (KDR), which had previously been reported to be up-regulated in vessels during colon cancer progression, was found to be expressed in both normal and neoplastic colorectal tissue (Fig. 3 D and E). The lack of specificity of this gene was in accord with the SAGE data, which indicated that the VEGFR was expressed at 12 copies per cell in both normal and tumor endothelium.

EXAMPLE 5

Tumor *versus* normal endothelium

- [131] We next attempted to identify transcripts that were differentially expressed in endothelium derived from normal or neoplastic tissues. This comparison revealed 33 tags that were preferentially expressed in normal-derived endothelium at levels at least 10-fold higher than in tumor-derived endothelium. Conversely, 46 tags were expressed at 10-fold or higher levels in tumor vessels. Because those transcripts expressed at higher levels in tumor endothelium are most likely to be useful in the future for diagnostic and therapeutic purposes, our subsequent studies focussed on this class. Of the top 25 tags most differentially expressed, 12 tags corresponded to 11 previously identified genes, one with an alternative polyadenylation site (see Table 2). Of these 10 genes, 6 have been recognized as markers associated with angiogenic vessels. The remaining 14 tags corresponded

to uncharacterised genes, most of which have only been deposited as ESTs (Table 2).

[132] To validate the expression patterns of these genes, we chose to focus on 9 Tumor Endothelial Markers (BSC-TEM 1-9; TEM 1, 2, 5, 9, 16, 17, 19, and 22) for which EST sequences but no other information was available (Table 2). These tags were chosen simply because they were among the most differentially expressed on the list and because we were able to obtain suitable probes. In many cases, this required obtaining near full-length sequences through multiple rounds of sequencing and cDNA walking (See accession numbers in Table 2). RT-PCR analysis was then used to evaluate the expression of the corresponding transcripts in purified ECs derived from normal and tumor tissues of two patients different from the one used to construct the SAGE libraries. As shown in Fig. 4 A, the vWF gene, expected to be expressed in both normal and tumor endothelium on the basis of the SAGE data as well as previous studies, was expressed at similar levels in normal and tumor ECs from both patients, but was not expressed in purified tumor epithelial cells. As expected, PEM2 displayed a pattern similar to vWF. In contrast, all 9 TEMs chosen for this analysis were prominently expressed in tumor ECs, but were absent or barely detectable in normal ECs (Table 3 and examples in Fig. 4A). It is important to note that these RT-PCR assays were extremely sensitive indicators of expression, and the absence of detectable transcripts in the normal endothelium, combined with their presence in tumor endothelial RNAs even when diluted 100-fold, provides compelling confirmatory evidence for their differential expression. These results also show that these transcripts were not simply expressed differentially in the ECs of the original patient, but were characteristic of colorectal cancer endothelium in general.

[133] It could be argued that the results noted above were compromised by the possibility that a small number of non-endothelial cells contaminated the cell populations used for SAGE and RT-PCR analyses, and that these non-endothelial

cells were responsible for the striking differences in expression of the noted transcripts. To exclude this possibility, we performed in situ hybridization on normal and neoplastic colon tissue. In every case where transcripts could be detected (BSC-TEM 1, 3, 4, 5, 7, 8, and 9; TEM 1, 5, 9, 17, and 19), they were specifically localized to ECs (Table 3 and examples in Fig. 4 B and C). Although caution must be used when interpreting negative in situ hybridization results, none of the TEMs were expressed in vascular ECs associated with normal colorectal tissue even though vWF and Hevin were clearly expressed (Table 3).

EXAMPLE 6

Tumor endothelium markers are expressed in multiple tumor types

- [134] Were these transcripts specifically expressed in the endothelium within primary colorectal cancers, or were they characteristic of tumor endothelium in general? To address this question, we studied the expression of a representative TEM (BSC-TEM7; TEM 17) in a liver metastasis from a colorectal cancer, a sarcoma, and in primary cancers of the lung, pancreas, breast and brain. As shown in Fig. 4, the transcript was found to be expressed specifically in the endothelium of each of these cancers, whether metastatic (Fig. 4D) or primary (Fig. 4E-I). Analysis of the other six TEMs, (BSC-TEM 1, 3, 4, 5, 7, 8 and 9; TEM 1, 5, 9, 17, and 19) revealed a similar pattern in lung tumors, brain tumors, and metastatic lesions of the liver (see Table 3).

EXAMPLE 7

Tumor endothelium markers are neo-angiogenic

- [135] Finally, we asked whether these transcripts were expressed in angiogenic states other than that associated with tumorigenesis. We thus performed in situ hybridizations on corpus luteum tissue as well as healing wounds. Although there

were exceptions, we found that these transcripts were generally expressed both in the corpus luteum and in the granulation tissue of healing wounds (Table 3 and example in Fig. 4J). In all tissues studied, expression of the genes was either absent or exclusively confined to the EC compartment.

References and Notes

The disclosure of each reference cited is expressly incorporated herein.

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8. The original EC isolation protocol was the same as that shown in Fig. 2B except that dispersed cells were stained with anti-CD31 antibodies instead of anti-P1H12, and magnetic beads against CD64 and CD14 were not included in the negative selection. After generating 120,000 SAGE tags from these two EC preparations, careful analysis of the SAGE data revealed that, in addition to endothelial-specific markers, several macrophage-specific markers were also present.
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11. In order to reduce the minimum amount of starting material required from ~50 million cells to ~50,000 cells (i.e. ~1000-fold less) we and others (38) have introduced

several modifications to the original SAGE protocol. A detailed version of our modified "MicroSAGE" protocol is available from the authors upon request.

12. 96,694 and 96,588 SAGE tags were analyzed from normal and tumor derived ECs, respectively, and represented 50,298 unique tags. A conservative estimate of 32,703 unique transcripts was derived by considering only those tags observed more than once in the current data set or in the 134,000 transcripts previously identified in human transcriptomes (39).

13. To identify endothelial specific transcripts, we normalized the number of tags analyzed in each group to 100,000, and limited our analysis to transcripts that were expressed at levels at least 20-fold higher in ECs than in non-endothelial cell lines in culture and present at fewer than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic fraction (~57,000 tags)(41). Non-endothelial cell lines consisted of 1.8x10⁶ tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. A complete list of PEMs is available at www.sagenet.org/angio/table1.htm.

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26. For non-radioactive in situ hybridization, digoxigenin (DIG)-labelled sense and anti-sense riboprobes were generated through PCR by amplifying 500-600 bp products and incorporating a T7 promoter into the anti-sense primer. In vitro transcription was performed using DIG RNA labelling reagents and T7 RNA polymerase (Roche, Indianapolis, IN). Frozen tissue sections were fixed with 4 % paraformaldehyde, permeabilized with pepsin, and incubated with 200 ng/ml of riboprobe overnight at 55°C. For signal amplification, a horseradish peroxidase (HRP) rabbit anti-DIG antibody (DAKO, Carpinteria, CA) was used to catalyse the deposition of Biotin-Tyramide (from GenPoint kit, DAKO). Further amplification was achieved by adding HRP rabbit anti-biotin (DAKO), biotin-tyramide, and then alkaline-phosphatase (AP) rabbit anti-biotin (DAKO). Signal was detected using the AP substrate Fast Red TR/Napthol AS-MX (Sigma, St. Louis, MO), and cells were counterstained with hematoxylin unless otherwise indicated. A detailed protocol including the list of primers used to generate the probes can be obtained from the authors upon request.
27. Transcript copies per cell were calculated assuming an average cell contains 300,000 transcripts.

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31. Endothelial-specific transcripts were defined as those expressed at levels at least 5-fold higher in ECs in vivo than in non-endothelial cell lines in culture (13), and present at no more than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic cell fraction (41). Transcripts showing statistically different levels of expression ($P < 0.05$) were then identified using Monte Carlo analysis as previously described (40). Transcripts preferentially expressed in normal endothelium were then defined as those expressed at levels at least 10-fold higher in normal endothelium than in tumor endothelium. Conversely, tumor endothelial transcripts were at least 10-fold higher in tumor versus normal endothelium. See www.sagenet.org/angio/table2.htm and www.sagenet.org/angio/table3.htm for a complete list of differentially expressed genes.
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Sequence name	SEQ ID NO:
PEM 1	1
PEM 2	2
PEM 3	3
PEM 4	4
PEM 5	5
PEM 6	6
PEM 7	7
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PEM 15	15
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TEM 5 Protein	188
TEM 7B Protein	189
mTEM 1 Protein	190
mTEM 5 Protein	191

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177	TEM 1 Protein
178	TEM 2 Protein
179	TEM 8 Protein
180	TEM 5 DNA
181	TEM 7B DNA
182	mTEM 1 DNA
183	mTEM 5 DNA
184	mTEM 7 DNA
185	mTEM 7B DNA
186	mTEM 8 DNA
187	TEM 8 Protein
188	TEM 5 Protein
189	TEM 7B Protein
190	mTEM 1 Protein
191	mTEM 5 Protein

mTEM 7 Protein	192
mTEM 7b Protein	193
mTEM 8 Protein	194
TEM 1 DNA	195
TEM 1 Protein	196
TEM 2 DNA	197
TEM 2 Protein	198
TEM 3 DNA	199
TEM 3 Protein	200
TEM 4 DNA	201
TEM 4 Protein	202
TEM 5 DNA	203
TEM 5 Protein	204
TEM 6 DNA	205
TEM 6 Protein	206
TEM 7 DNA	207
TEM 7 Protein	208
TEM 8 DNA	209
TEM 8 Protein	210
TEM 9 DNA	211
TEM 9 Protein	212
TEM 10 DNA	213
TEM 10 Protein	214
TEM 11 DNA	215
TEM 11 Protein	216
TEM 12 DNA	217
TEM 12 Protein	218
TEM 13 DNA	219
TEM 13 Protein	220
TEM 14a DNA	221
TEM 14b DNA	222
TEM 14a Protein	223
TEM 14b Protein	224
TEM 15 DNA	225
TEM 15 Protein	226
TEM 16 DNA	227
TEM 16 Protein	228
TEM 17 DNA	229
TEM 17 Protein	230

192	mTEM 7 Protein
193	mTEM 7b Protein
194	mTEM 8 Protein
195	TEM 1 DNA
196	TEM 1 Protein
197	TEM 2 DNA
198	TEM 2 Protein
199	TEM 3 DNA
200	TEM 3 Protein
201	TEM 4 DNA
202	TEM 4 Protein
203	TEM 5 DNA
204	TEM 5 Protein
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207	TEM 7 DNA
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222	TEM 14b DNA
223	TEM 14a Protein
224	TEM 14b Protein
225	TEM 15 DNA
226	TEM 15 Protein
227	TEM 16 DNA
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229	TEM 17 DNA
230	TEM 17 Protein

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TEM 20 DNA	233
TEM 20 Protein	234
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TEM 22 Protein	238
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TEM 31 Protein	252
TEM 33 DNA	253
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TEM 35 Protein	358
TEM 36 DNA	256
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TEM 37 Protein	259
TEM 38 DNA	260
TEM 38 Protein	261
TEM 39 DNA	262
TEM 39 Protein	263
TEM 40 DNA	264
TEM 40 Protein	265
TEM 41 DNA	266
TEM 41 Protein	267
TEM 42 DNA	268

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233	TEM 20 DNA
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262	TEM 39 DNA
263	TEM 39 Protein
264	TEM 40 DNA
265	TEM 40 Protein
266	TEM 41 DNA
267	TEM 41 Protein
268	TEM 42 DNA
269	TEM 42 Protein

TEM 42 Protein	269
TEM 44 DNA	270
TEM 44 Protein	271
TEM 45 DNA	272
TEM 45 Protein	273
TEM 46 DNA	274
TEM 46 Protein	275
NEM 4 DNA	276
NEM 4 Protein	277
NEM 14 DNA	278
NEM 14 Protein	279
NEM 17 DNA	280
NEM 17 Protein	281
NEM 22 DNA	282
NEM 22 Protein	283
NEM 23 DNA	284
NEM 23 Protein	285
NEM 23 Secreted	286
NEM 23 Short	287
NEM 33 DNA	288
NEM 33 Protein	289
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mTEM 3 Protein	299
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mTEM 17 Protein	297
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mTEM 22 Protein	305
mTEM 30 DNA	306
mTEM 30 Protein	307

270	TEM 44 DNA
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272	TEM 45 DNA
273	TEM 45 Protein
274	TEM 46 DNA
275	TEM 46 Protein
276	NEM 4 DNA
277	NEM 4 Protein
278	NEM 14 DNA
279	NEM 14 Protein
280	NEM 17 DNA
281	NEM 17 Protein
282	NEM 22 DNA
283	NEM 22 Protein
284	NEM 23 DNA
285	NEM 23 Protein
286	NEM 23 Secreted
287	NEM 23 Short
288	NEM 33 DNA
289	NEM 33 Protein
290	mTEM 1 DNA
291	mTEM 1 Protein
292	mTEM 2 DNA
293	mTEM 2 Protein
294	mTEM 9 DNA
295	mTEM 9 Protein
296	mTEM 17 DNA
297	mTEM 17 Protein
298	mTEM 3 DNA
299	mTEM 3 Protein
300	mTEM 19 DNA
301	mTEM 19 Protein
302	mTEM 13 DNA
303	mTEM 13 Protein
304	mTEM 22 DNA
305	mTEM 22 Protein
306	mTEM 30 DNA
307	mTEM 30 Protein
308	TEM 2 tag

TEM 2 tag	308
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TEM 5 long tag	312
TEM 5 long tag	313
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TEM 33 long tag	344
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TEM 36 long tag	346

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323	TEM 13 long tag
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325	TEM 14 long tag
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343	TEM 33 long tag
344	TEM 33 long tag
345	TEM 35 long tag
346	TEM 36 long tag
347	TEM 37 long tag

TEM 37 long tag	347
TEM 38 long tag	348
TEM 38 long tag	349
TEM 39 long tag	350
TEM 40 long tag	351
TEM 41 long tag	352
TEM 42 long tag	353
TEM 43 long tag	354
TEM 44 long tag	355
TEM 45 long tag	356
TEM 46 long tag	357

348	TEM 38 long tag
349	TEM 38 long tag
350	TEM 39 long tag
351	TEM 40 long tag
352	TEM 41 long tag
353	TEM 42 long tag
354	TEM 43 long tag
355	TEM 44 long tag
356	TEM 45 long tag
357	TEM 46 long tag
358	TEM 35 Protein

CLAIMS

1. An isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively.
2. The isolated molecule of claim 1 which is an intact antibody molecule.
3. The isolated molecule of claim 1 which is a single chain variable region (ScFv).
4. The isolated molecule of claim 1 which is a monoclonal antibody.
5. The isolated molecule of claim 1 which is a humanized antibody.
6. The isolated molecule of claim 1 which is a human antibody.
7. The isolated molecule of claim 1 which is bound to a cytotoxic moiety.
8. The isolated molecule of claim 1 which is bound to a therapeutic moiety.
9. The isolated molecule of claim 1 which is bound to a detectable moiety.
10. The isolated molecule of claim 1 which is bound to an anti-tumor agent.

11. A method of inhibiting neoangiogenesis, comprising:
administering to a subject in need thereof an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby neoangiogenesis is inhibited.
12. The method of claim 11 wherein the subject bears a vascularized tumor.
13. The method of claim 11 wherein the subject has polycystic kidney disease.
14. The method of claim 11 wherein the subject has diabetic retinopathy.
15. The method of claim 11 wherein the subject has rheumatoid arthritis.
16. The method of claim 11 wherein the subject has psoriasis.

17. A method of inhibiting tumor growth, comprising:

administering to a human subject bearing a tumor an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, 238, and 271, respectively, whereby growth of the tumor is inhibited.

18. An isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 9, 17, 19, and 44, as shown in SEQ ID NO: 212, 230, 232, and 271, respectively.

19. The isolated molecule of claim 18 which is a single chain variable region (ScFv).

20. The isolated molecule of claim 18 which is a monoclonal antibody.

21. The isolated molecule of claim 18 which is a humanized antibody.

22. The isolated molecule of claim 18 which is a human antibody.

23. The isolated molecule of claim 18 which is bound to a cytotoxic moiety.

24. The isolated molecule of claim 18 which is bound to a therapeutic moiety.

25. The isolated molecule of claim 18 which is bound to a detectable

moiety.

26. The isolated molecule of claim 18 which is bound to an anti-tumor agent.
27. The isolated molecule of claim 18 which is an intact antibody molecule.
28. An isolated and purified human transmembrane protein selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
29. An isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, 232, respectively.
30. The isolated and purified nucleic acid molecule of claim 29 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231,.
31. A recombinant host cell which comprises a nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: TEM 9, 17, and 19 as shown in SEQ ID NO: 212, 230, and 232, respectively.
32. The recombinant host cell of claim 31 which comprises a coding sequence selected from those shown in SEQ ID NO: 211, 229, and 231.
33. A method of inducing an immune response in a mammal, comprising:
administering to the mammal a nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.

34. The method of claim 33 wherein the coding sequence is shown in SEQ ID NO: 195, 211, 219, 229, 231, 237, 249, 270.
35. A method of inducing an immune response in a mammal, comprising:
administering to the mammal a purified human transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271, respectively, whereby an immune response to the human transmembrane protein is induced in the mammal.
36. A method for identification of a ligand involved in endothelial cell regulation, comprising:
contacting a test compound with an isolated and purified human transmembrane protein selected from the group consisting of 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271;
contacting the isolated and purified human transmembrane protein with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 250, 232 and 271, respectively;
determining binding of the molecule comprising an antibody variable region to the human transmembrane protein, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.
37. A method for identification of a ligand involved in endothelial cell regulation, comprising:
contacting a test compound with a cell comprising a human transmembrane protein selected from the group consisting of 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232;

contacting the cell with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, and 19 as shown in SEQ ID NO: 196, 212, 230, and 232, respectively;

determining binding of the molecule comprising an antibody variable region to the cell, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

38. A soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 9, 17, 19, 22, 30 and 44 as shown in SEQ ID NO: 196, 212, 230, 232, 238, 250, and 271, respectively, wherein the soluble forms lack transmembrane domains.

39. The soluble form of claim 38 wherein the soluble form consists of an extracellular domain of the human transmembrane protein.

40. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 38, whereby neoangiogenesis in the patient is inhibited.

41. A method of inhibiting neoangiogenesis in a patient, comprising: administering to the patient a soluble form of a human transmembrane protein according to claim 39, whereby neoangiogenesis in the patient is inhibited.

42. The method of claim 40 wherein the patient bears a vascularized tumor.

43. The method of claim 41 wherein the patient bears a vascularized tumor.

44. The method of claim 40 wherein the patient has polycystic kidney disease.
45. The method of claim 40 wherein the patient has diabetic retinopathy.
46. The method of claim 40 wherein the patient has rheumatoid arthritis.
47. The method of claim 40 wherein the patient has psoriasis.
48. The method of claim 41 wherein the patient has polycystic kidney disease.
49. The method of claim 41 wherein the patient has diabetic retinopathy.
50. The method of claim 41 wherein the patient has rheumatoid arthritis.
51. The method of claim 41 wherein the patient has psoriasis.
52. A method of identifying regions of neoangiogenesis in a patient, comprising:
administering to a patient a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250, and 271, respectively, wherein the molecule is bound to a detectable moiety; and
detecting the detectable moiety in the patient, thereby identifying neoangiogenesis.
53. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 212, 230, 232, and 271, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

54. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 25, 27, 31, 36, 37, 38, 39, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 242, 244, 252, 257, 259, 261, and 263, respectively, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

55. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, whereby neoangiogenesis in the patient is stimulated.

56. A method of promoting neoangiogenesis in a patient, comprising:

administering to a patient in need of neoangiogenesis a nucleic acid molecule encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, whereby the TEM protein is expressed and neoangiogenesis in the patient is stimulated.

57. A method of screening for neoangiogenesis in a patient, comprising:

detecting a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261, 263, and 265, respectively, in a body fluid collected from the patient, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

58. A method of screening for neoangiogenesis in a patient, comprising:

detecting in a body fluid collected from the patient a nucleic acid encoding a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, wherein the nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, respectively, wherein detection of the TEM protein indicates neoangiogenesis in the patient.

59. An isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

60. The nucleic acid molecule of claim 60 wherein the nucleic acid molecule comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288.

61. A recombinant host cell which comprises a nucleic acid according to claim 60.

62. An isolated and purified NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, respectively.

63. An isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group

consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

64. A method of inhibiting neoangiogenesis, comprising:

administering to a subject in need thereof an effective amount of a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, whereby neoangiogenesis is inhibited.

65. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM genes selected from the group consisting of: 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 195, 197, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, with a test compound;

determining expression of said one or more TEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes.

66. The method of claim 66 wherein the cells are endothelial cells.

67. The method of claim 66 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

68. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41,

42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, with a test compound;

determining amount of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the amount of one more TEM proteins in said cells.

69. The method of claim 69 wherein the cells are endothelial cells.

70. The method of claim 69 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

71. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more TEM proteins selected from the group consisting of: 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 respectively, with a test compound;

determining activity of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the activity of of one more TEM proteins in said cells.

72. The method of claim 72 wherein the cells are endothelial cells.

73. The method of claim 72 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

74. A method to identify candidate drugs for treating patients bearing tumors, comprising:

contacting a test compound with recombinant host cells which are transfected with an expression construct which encodes one or more TEM proteins selected from the group consisting of 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively;

determining proliferation of said cells; and

identifying a test compound which inhibits proliferation of said cells as a candidate drug for treating patients bearing tumors.

75. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, with a test compound;

determining expression of said one or more NEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it increases expression of said one or more NEM genes.

76. The method of claim 76 wherein the cells are endothelial cells.

77. The method of claim 76 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

78. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;

determining amount of said one or more NEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells.

79. The method of claim 79 wherein the cells are endothelial cells.

80. The method of claim 79 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

81. A method to identify candidate drugs for treating tumors, comprising:
- contacting cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, with a test compound;
 - determining activity of said one or more NEM proteins in said cells; and
 - identifying a test compound as a candidate drug for treating tumors if it increases the activity of one more NEM proteins in said cells.
82. The method of claim 82 wherein the cells are endothelial cells.
83. The method of claim 82 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.
84. A method to identify candidate drugs for treating patients bearing tumors, comprising:
- contacting a test compound with recombinant host cells which are transfected with an expression construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289;
 - determining proliferation of said cells; and
 - identifying a test compound which stimulates proliferation of said cells as a candidate drug for treating patients bearing tumors.
85. A method for identification of a ligand involved in endothelial cell regulation, comprising:
- contacting a test compound with a human transmembrane TEM protein selected from the group consisting of 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196,

198, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275;

determining binding of a test compound to the human transmembrane protein, wherein a test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

86. A method of inducing an immune response in a mammal, comprising:
administering to the mammal a cell which expresses a transmembrane protein selected from the group consisting of: TEM 1, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 212, 220, 230, 232, 238, 250 and 271 , respectively, wherein the cell is a recombinant cell which comprises a vector encoding said transmembrane protein, or the cell is a fusion of a dendritic cell and a tumor endothelium cell, whereby an immune response to the human transmembrane protein is induced in the mammal.

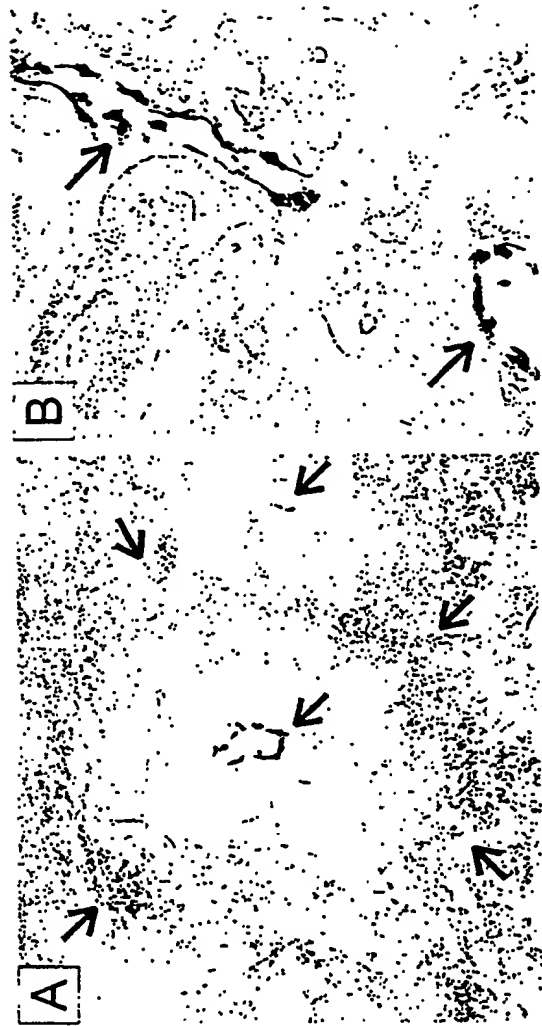
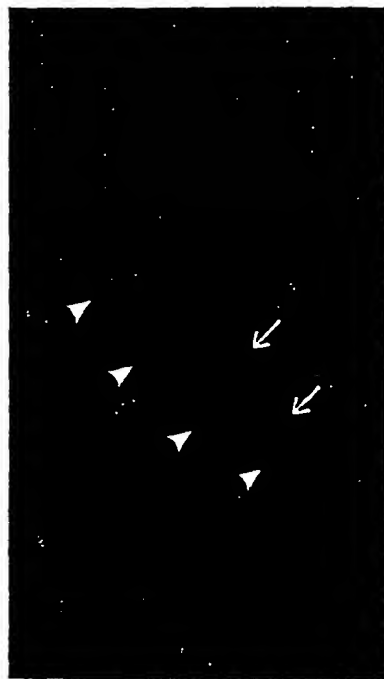
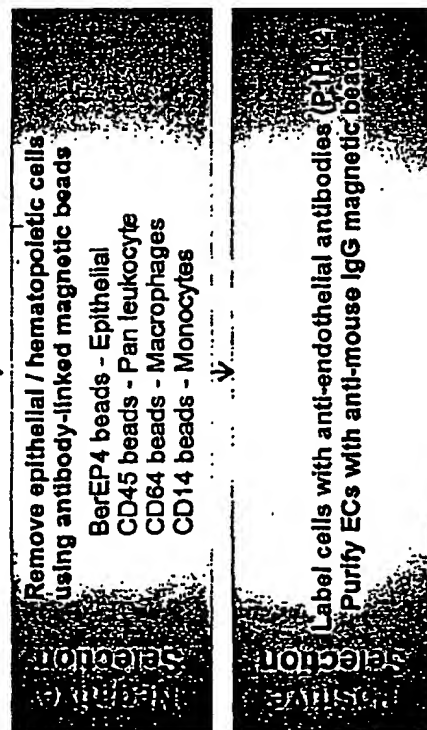
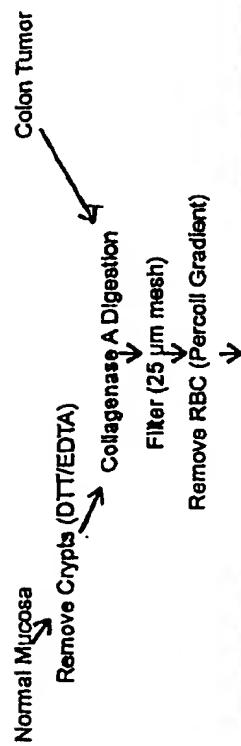


Figure 1

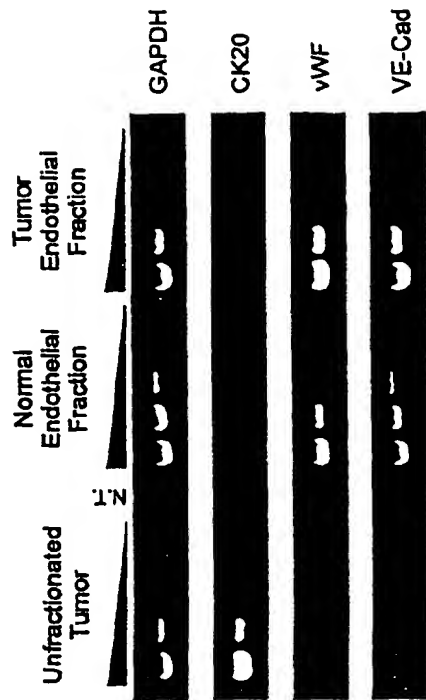
A



B



C



D

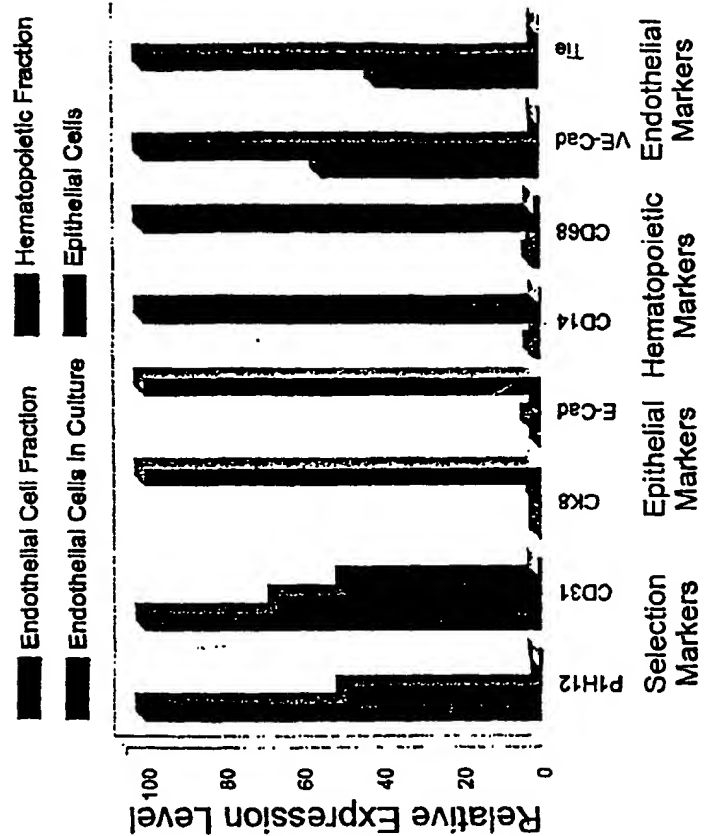


Figure 2

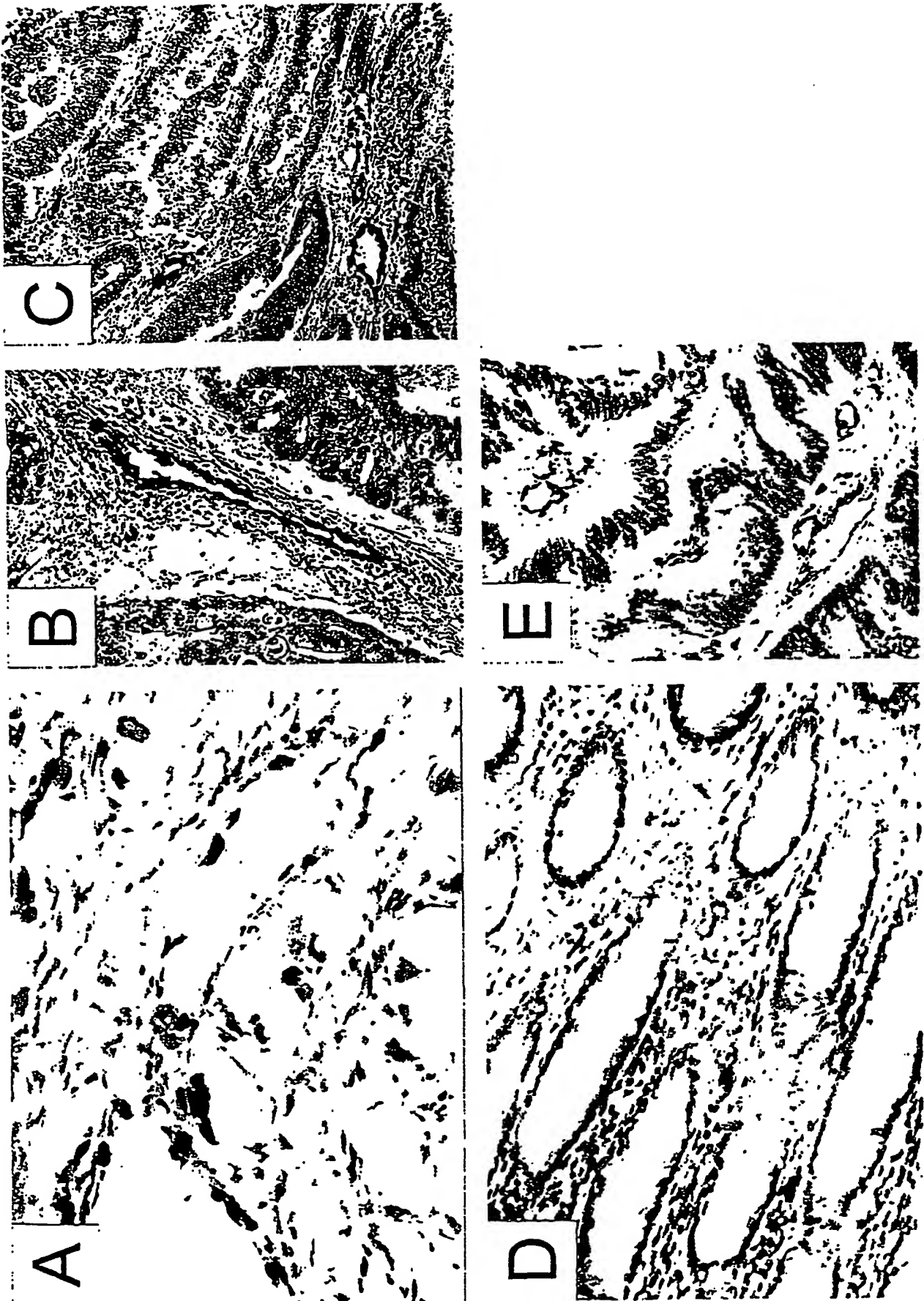


Figure 3

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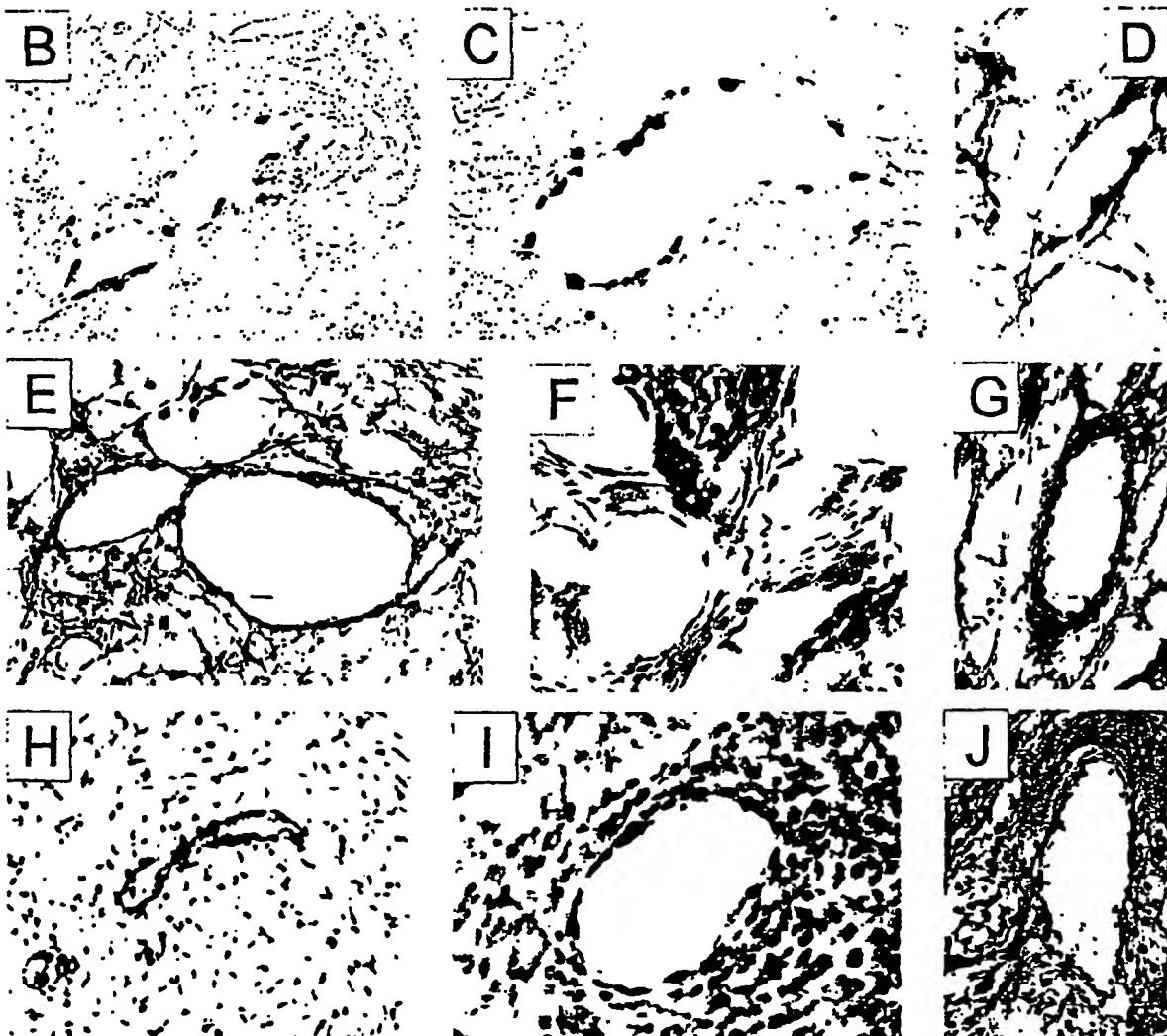
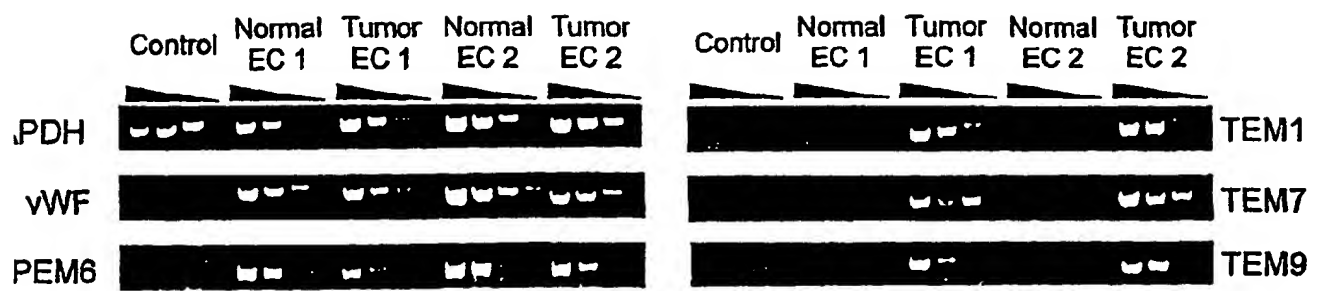


Figure 4

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<210> 177
 <211> 757
 <212> PRT
 <213> Homo sapiens

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Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
 35          40          45
Arg Ala Cys Arg Glu Leu Gly Gly Asp Leu Ala Thr Pro Arg Thr Pro
 50          55          60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Ala Gly Pro Ala Ser
 65          70          75          80
Arg Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Leu
 85          90          95
Gln Arg Pro Leu Arg Gly Phe Thr Trp Thr Thr Gly Asp Gln Asp Thr
100          105          110
Ala Phe Thr Asn Trp Ala Gln Pro Ala Ser Gly Gly Pro Cys Pro Ala
115          120          125
Gln Arg Cys Val Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
130          135          140
Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
145          150          155          160
Glu Gly Ala Cys Pro Ala Leu Gln Asp Glu Ala Gly Gln Ala Gly Pro
165          170          175
Ala Val Tyr Thr Thr Pro Phe His Leu Val Ser Thr Glu Phe Glu Trp
180          185          190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly

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Arg	Ala	Gly	Pro	Leu	Cys	Leu	Gly	Thr	Gly	Cys	Ser	Pro	Asp	Asn	Gly
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Gly	Cys	Glu	His	Glu	Cys	Val	Glu	Glu	Val	Asp	Gly	His	Val	Ser	Cys
				245					250					255	
Arg	Cys	Thr	Glu	Gly	Phe	Arg	Leu	Ala	Ala	Asp	Gly	Arg	Ser	Cys	Glu
			260					265					270		
Asp	Pro	Cys	Ala	Gln	Ala	Pro	Cys	Glu	Gln	Gln	Cys	Glu	Pro	Gly	Gly
		275					280					285			
Pro	Gln	Gly	Tyr	Ser	Cys	His	Cys	Arg	Leu	Gly	Phe	Arg	Pro	Ala	Glu
		290				295					300				
Asp	Asp	Pro	His	Arg	Cys	Val	Asp	Thr	Asp	Glu	Cys	Gln	Ile	Ala	Gly
305					310					315					320
Val	Cys	Gln	Gln	Met	Cys	Val	Asn	Tyr	Val	Gly	Gly	Phe	Glu	Cys	Tyr
				325					330					335	
Cys	Ser	Glu	Gly	His	Glu	Leu	Glu	Ala	Asp	Gly	Ile	Ser	Cys	Ser	Pro
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Ala	Gly	Ala	Met	Gly	Ala	Gln	Ala	Ser	Gln	Asp	Leu	Gly	Asp	Glu	Leu
		355					360					365			
Leu	Asp	Asp	Gly	Glu	Asp	Glu	Glu	Asp	Glu	Asp	Glu	Ala	Trp	Lys	Ala
		370				375					380				
Phe	Asn	Gly	Gly	Trp	Thr	Glu	Met	Pro	Gly	Ile	Leu	Trp	Met	Glu	Pro
385					390					395					400
Thr	Gln	Pro	Pro	Asp	Phe	Ala	Leu	Ala	Tyr	Arg	Pro	Ser	Phe	Pro	Glu
				405					410					415	
Asp	Arg	Glu	Pro	Gln	Ile	Pro	Tyr	Pro	Glu	Pro	Thr	Trp	Pro	Pro	Pro
			420					425					430		
Leu	Ser	Ala	Pro	Arg	Val	Pro	Tyr	His	Ser	Ser	Val	Leu	Ser	Val	Thr
		435					440					445			
Arg	Pro	Val	Val	Val	Ser	Ala	Thr	His	Pro	Thr	Leu	Pro	Ser	Ala	His
		450				455					460				
Gln	Pro	Pro	Val	Ile	Pro	Ala	Thr	His	Pro	Ala	Ser	Arg	Asp	His	
465					470					475				480	
Gln	Ile	Pro	Val	Ile	Ala	Ala	Asn	Tyr	Pro	Asp	Leu	Pro	Ser	Ala	Tyr
				485					490					495	
Gln	Pro	Gly	Ile	Leu	Ser	Val	Ser	His	Ser	Ala	Gln	Pro	Pro	Ala	His
			500					505					510		
Gln	Pro	Pro	Met	Ile	Ser	Thr	Lys	Tyr	Pro	Glu	Leu	Phe	Pro	Ala	His
			515				520					525			
Gln	Ser	Pro	Met	Phe	Pro	Asp	Thr	Arg	Val	Ala	Gly	Thr	Gln	Thr	Thr
		530				535									

Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
 690 695 700
 Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
 705 710 715 720
 Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
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 Pro Thr Glu Pro Met Pro Pro Arg Gly Ser Leu Thr Gly Val Gln Thr
 740 745 750
 Cys Arg Thr Ser Val
 755

<210> 178
 <211> 278
 <212> PRT
 <213> Homo sapiens

<400> 178
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 20 25 30
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 35 40 45
 Ser Arg Phe Leu Asn Gly Arg Phe Glu Asp Gln Tyr Thr Pro Thr Ile
 50 55 60
 Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly Asp Met Tyr Gln
 65 70 75 80
 Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe Pro Ala Met Arg
 85 90 95
 Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu Val Phe Ser Leu
 100 105 110
 Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu Gln Lys Gln Ile
 115 120 125
 Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys Glu Ala Ala Glu
 130 135 140
 Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His Gly Glu Leu Cys
 145 150 155 160
 Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val Ser Gly Asp Glu
 165 170 175
 Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn Thr Asn Val Asp
 180 185 190
 Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu Pro His Glu Met
 195 200 205
 Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr Gly Asp Ala Phe
 210 215 220
 His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu Met Asp Ala Tyr
 225 230 235 240
 Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val Asn Ser Asp Leu
 245 250 255
 Lys Tyr Ile Lys Ala Lys Val Leu Arg Glu Gly Gln Ala Arg Glu Arg
 260 265 270
 Asp Lys Cys Thr Ile Gln
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<210> 179
 <211> 1002
 <212> PRT
 <213> Homo sapiens

<400> 179
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Ser Gly Trp Ala	Ala Lys Gly Thr	Val Arg Gly Trp	Asn Arg Arg Ala
35	40	45	
Arg Glu Ser Pro	Gly His Val Ser	Glu Pro Asp Arg	Thr Gln Leu Ser
50	55	60	
Gln Asp Leu Gly	Gly Gly Thr Leu	Ala Met Asp Thr	Leu Pro Asp Asn
65	70	75	80
Arg Thr Arg Val	Val Glu Asp Asn	His Ser Tyr Tyr	Val Ser Arg Leu
85	90	95	
Tyr Gly Pro Ser	Glu Pro His Ser	Arg Glu Leu Trp	Val Asp Val Ala
100	105	110	
Glu Ala Asn Arg	Ser Gln Val Lys	Ile His Thr Ile	Leu Ser Asn Thr
115	120	125	
His Arg Gln Ala	Ser Arg Val Val	Leu Ser Phe Asp	Phe Pro Phe Tyr
130	135	140	
Gly His Pro Leu	Arg Gln Ile Thr	Ile Ala Thr Gly	Gly Phe Ile Phe
145	150	155	160
Met Gly Asp Val	Ile His Arg Met	Leu Thr Ala Thr	Gln Tyr Val Ala
165	170	175	
Pro Leu Met Ala	Asn Phe Asn Pro	Gly Tyr Ser Asp	Asn Ser Thr Val
180	185	190	
Val Tyr Phe Asp	Asn Gly Thr Val	Phe Val Val Gln	Trp Asp His Val
195	200	205	
Tyr Leu Gln Gly	Trp Glu Asp Lys	Gly Ser Phe Thr	Phe Gln Ala Ala
210	215	220	
Leu His His Asp	Gly Arg Ile Val	Phe Ala Tyr Lys	Glu Ile Pro Met
225	230	235	240
Ser Val Pro Glu	Ile Ser Ser Ser	Gln His Pro Val	Lys Thr Gly Leu
245	250	255	
Ser Asp Ala Phe	Met Ile Leu Asn	Pro Ser Pro Asp	Val Pro Glu Ser
260	265	270	
Arg Arg Arg Ser	Ile Phe Glu Tyr	His Arg Ile Glu	Leu Asp Pro Ser
275	280	285	
Lys Val Thr Ser	Met Ser Ala Val	Glu Phe Thr Pro	Leu Pro Thr Cys
290	295	300	
Leu Gln His Arg	Ser Cys Asp Ala	Cys Met Ser Ser	Asp Leu Thr Phe
305	310	315	320
Asn Cys Ser Trp	Cys His Val Leu	Gln Arg Cys Ser	Ser Gly Phe Asp
325	330	335	
Arg Tyr Arg Gln	Glu Trp Asp Gly	Thr Met Gly Cys	Ala Gln Glu Ala
340	345	350	
Glu Gly Gln Asp	Val Arg Gly Leu	Pro Gly Met Arg	Thr Thr Thr Ser
355	360	365	
Ala Ser Pro Asp	Thr Ser Phe Ser	Pro Tyr Asp Gly	Asp Leu Thr Thr
370	375	380	
Thr Ser Ser Ser	Leu Phe Ile Asp	Ser Leu Thr Thr	Glu Asp Asp Thr
385	390	395	400
Lys Leu Asn Pro	Tyr Ala Gly Gly	Asp Gly Leu Gln	Asn Asn Leu Ser
405	410	415	
Pro Lys Thr Lys	Gly Thr Pro Val	His Leu Gly Thr	Ile Val Gly Ile
420	425	430	
Val Leu Ala Val	Leu Leu Val Ala	Ala Ala Ile Ile	Leu Ala Gly Ile
435	440	445	
Ile Asn Gly His	Pro Thr Ser Asn	Ala Ala Leu Phe	Phe Ile Glu Arg
450	455	460	
Arg Pro His His	Trp Pro Ala Met	Lys Phe Arg Ser	His Pro Asp His
465	470	475	480
Ser Thr Tyr Ala	Glu Val Glu Pro	Ser Gly His Glu	Lys Glu Gly Phe
485	490	495	

Met Glu Ala Glu Gln Cys Met Arg Gly Glu Leu Trp Leu Leu Val Leu
 500 505 510
 Val Leu Arg Glu Ala Ala Arg Ala Leu Ser Pro Gln Pro Gly Ala Gly
 515 520 525
 His Asp Glu Gly Pro Gly Ser Gly Trp Ala Ala Lys Gly Thr Val Arg
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 Gly Trp Asn Arg Arg Ala Arg Glu Ser Pro Gly His Val Ser Glu Pro
 545 550 555 560
 Asp Arg Thr Gln Leu Ser Gln Asp Leu Gly Gly Gly Thr Leu Ala Met
 565 570 575
 Asp Thr Leu Pro Asp Asn Arg Thr Arg Val Val Glu Asp Asn His Ser
 580 585 590
 Tyr Tyr Val Ser Arg Leu Tyr Gly Pro Ser Glu Pro His Ser Arg Glu
 595 600 605
 Leu Trp Val Asp Val Ala Glu Ala Asn Arg Ser Gln Val Lys Ile His
 610 615 620
 Thr Ile Leu Ser Asn Thr His Arg Gln Ala Ser Arg Val Val Leu Ser
 625 630 635 640
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 Thr Gly Gly Phe Ile Phe Met Gly Asp Val Ile His Arg Met Leu Thr
 660 665 670
 Ala Thr Gln Tyr Val Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr
 675 680 685
 Ser Asp Asn Ser Thr Val Val Tyr Phe Asp Asn Gly Thr Val Phe Val
 690 695 700
 Val Gln Trp Asp His Val Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser
 705 710 715 720
 Phe Thr Phe Gln Ala Ala Leu His His Asp Gly Arg Ile Val Phe Ala
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 Tyr Lys Glu Ile Pro Met Ser Val Pro Glu Ile Ser Ser Ser Gln His
 740 745 750
 Pro Val Lys Thr Gly Leu Ser Asp Ala Phe Met Ile Leu Asn Pro Ser
 755 760 765
 Pro Asp Val Pro Glu Ser Arg Arg Arg Ser Ile Phe Glu Tyr His Arg
 770 775 780
 Ile Glu Leu Asp Pro Ser Lys Val Thr Ser Met Ser Ala Val Glu Phe
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 Thr Pro Leu Pro Thr Cys Leu Gln His Arg Ser Cys Asp Ala Cys Met
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 Cys Ser Ser Gly Phe Asp Arg Tyr Arg Gln Glu Trp Met Asp Tyr Gly
 835 840 845
 Cys Ala Gln Glu Ala Glu Gly Arg Met Cys Glu Asp Phe Gln Asp Glu
 850 855 860
 Asp His Asp Ser Ala Ser Pro Asp Thr Ser Phe Ser Pro Tyr Asp Gly
 865 870 875 880
 Asp Leu Thr Thr Thr Ser Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr
 885 890 895
 Glu Asp Asp Thr Lys Leu Asn Pro Tyr Ala Gly Gly Asp Gly Leu Gln
 900 905 910
 Asn Asn Leu Ser Pro Lys Thr Lys Gly Thr Pro Val His Leu Gly Thr
 915 920 925
 Ile Val Gly Ile Val Leu Ala Val Leu Leu Val Ala Ala Ile Ile Leu
 930 935 940
 Ala Gly Ile Tyr Ile Asn Gly His Pro Thr Ser Asn Ala Ala Leu Phe
 945 950 955 960
 Phe Ile Glu Arg Arg Pro His His Trp Pro Ala Met Lys Phe Arg Ser
 965 970 975
 His Pro Asp His Ser Thr Tyr Ala Glu Val Glu Pro Ser Gly His Glu

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Lys Glu Gly Phe Met Glu Ala Glu Gln Cys
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990

<210> 180
<211> 5680
<212> DNA
<213> Homo sapiens

<400> 180

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<211> 2833

<212> DNA

<213> Mus musculus

<400> 184

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<211> 2009

<212> DNA

<213> Mus musculus

<400> 185

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<211> 5220

<212> DNA

<213> Mus musculus

<400> 186

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Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
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Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
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Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
180    185    190
Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
195    200    205
Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
210    215    220
Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
225    230    235    240
Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
245    250    255
Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
260    265    270
Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
275    280    285
Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
290    295    300
Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
305    310    315    320
Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
325    330    335
Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
340    345    350
Glu Val Pro Pro Pro Ala Glu Glu Ser Glu Glu Glu Asp Asp Asp
355    360    365
Gly Leu Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly

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370		375		380
Gly Arg Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu				
385		390		395
Lys Gly Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala				
	405		410	415
Arg Val Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn				
	420	425		430
Leu Asn Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser		440	445	
	435			460
Pro Ile Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly		455		
	450			
Tyr Asp Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg			475	480
465		470		
Cys Ile Asn Phe Thr Arg Val Lys Asn Asn Gln Pro Ala Lys Tyr Pro			490	495
	485			
Leu Asn Asn Ala Tyr His Thr Ser Ser Pro Pro Pro Ala Pro Ile Tyr		505		510
	500			
Thr Pro Pro Pro Pro Ala Pro His Cys Pro Pro Pro Pro Ser Ala		520	525	
	515			
Pro Thr Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro		535	540	
	530			
Gln Ala Pro Pro Pro Asn Arg Ala Pro Pro Pro Ser Arg Pro Pro Pro			555	560
545		550		
Arg Pro Ser Val				

<210> 188
 <211> 1331
 <212> PRT
 <213> Homo sapiens

<400> 188
Met Arg Gly Ala Pro Ala Arg Leu Leu Leu Pro Leu Leu Pro Trp Leu
1 5 10 15
Leu Leu Leu Leu Ala Pro Glu Ala Arg Gly Ala Pro Gly Cys Pro Leu
20 25 30
Ser Ile Arg Ser Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
35 40 45
Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
50 55 60
Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
65 70 75 80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
85 90 95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
100 105 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
115 120 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
130 135 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145 150 155 160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
165 170 175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
180 185 190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
195 200 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
210 215 220
Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr

225					230					235				240
His	His	Leu	Ile	Pro	Ser	Leu	Arg	Gln	Val	Val	Phe	Gln	Gly	Asp Arg
				245					250					255
Leu	Pro	Phe	Gln	Cys	Ser	Ala	Ser	Tyr	Leu	Gly	Asn	Asp	Thr	Arg Ile
			260					265					270	
Arg	Trp	Tyr	His	Asn	Arg	Ala	Pro	Val	Glu	Gly	Asp	Glu	Gln	Ala Gly
		275					280					285		
Ile	Leu	Leu	Ala	Glu	Ser	Leu	Ile	His	Asp	Cys	Thr	Phe	Ile	Thr Ser
	290					295					300			
Glu	Leu	Thr	Leu	Ser	His	Ile	Gly	Val	Trp	Ala	Ser	Gly	Glu	Trp Glu
305					310					315				320
Cys	Thr	Val	Ser	Met	Ala	Gln	Gly	Asn	Ala	Ser	Lys	Lys	Val	Glu Ile
				325					330					335
Val	Val	Leu	Glu	Thr	Ser	Ala	Ser	Tyr	Cys	Pro	Ala	Glu	Arg	Val Ala
			340					345					350	
Asn	Asn	Arg	Gly	Asp	Phe	Arg	Trp	Pro	Arg	Thr	Leu	Ala	Gly	Ile Thr
		355					360					365		
Ala	Tyr	Gln	Ser	Cys	Leu	Gln	Tyr	Pro	Phe	Thr	Ser	Val	Pro	Leu Gly
	370					375					380			
Gly	Gly	Ala	Pro	Gly	Thr	Arg	Ala	Ser	Arg	Arg	Cys	Asp	Arg	Ala Gly
385					390					395				400
Arg	Trp	Glu	Pro	Gly	Asp	Tyr	Ser	His	Cys	Leu	Tyr	Thr	Asn	Asp Ile
				405					410					415
Thr	Arg	Val	Leu	Tyr	Thr	Phe	Val	Leu	Met	Pro	Ile	Asn	Ala	Ser Asn
			420					425					430	
Ala	Leu	Thr	Leu	Ala	His	Gln	Leu	Arg	Val	Tyr	Thr	Ala	Glu	Ala Ala
	435						440					445		
Ser	Phe	Ser	Asp	Met	Met	Asp	Val	Val	Tyr	Val	Ala	Gln	Met	Ile Gln
	450					455					460			
Lys	Phe	Leu	Gly	Tyr	Val	Asp	Gln	Ile	Lys	Glu	Leu	Val	Glu	Val Met
465					470					475				480
Val	Asp	Met	Ala	Ser	Asn	Leu	Met	Leu	Val	Asp	Glu	His	Leu	Leu Trp
				485					490					495
Leu	Ala	Gln	Arg	Glu	Asp	Lys	Ala	Cys	Ser	Arg	Ile	Val	Gly	Ala Leu
			500					505					510	
Glu	Arg	Ile	Gly	Gly	Ala	Ala	Leu	Ser	Pro	His	Ala	Gln	His	Ile Ser
		515					520					525		
Val	Asn	Ala	Arg	Asn	Val	Ala	Leu	Glu	Ala	Tyr	Leu	Ile	Lys	Pro His
	530					535					540			
Ser	Tyr	Val	Gly	Leu	Thr	Cys	Thr	Ala	Phe	Gln	Arg	Arg	Glu	Gly Gly
545					550					555				560
Val	Pro	Gly	Thr	Arg	Pro	Gly	Ser	Pro	Gly	Gln	Asn	Pro	Pro	Pro Glu
				565					570					575
Pro	Glu	Pro	Pro	Ala	Asp	Gln	Gln	Leu	Arg	Phe	Arg	Cys	Thr	Thr Gly
			580					585					590	
Arg	Pro	Asn	Val	Ser	Leu	Ser	Ser	Phe	His	Ile	Lys	Asn	Ser	Val Ala
		595					600					605		
Leu	Ala	Ser	Ile	Gln	Leu	Pro	Pro	Ser	Leu	Phe	Ser	Ser	Leu	Pro Ala
	610					615					620			
Ala	Leu	Ala	Pro	Pro	Val	Pro	Pro	Asp	Cys	Thr	Leu	Gln	Leu	Leu Val
625					630					635				640
Phe	Arg	Asn	Gly	Arg	Leu	Phe	His	Ser	His	Ser	Asn	Thr	Ser	Arg Pro
				645					650					655
Gly	Ala	Ala	Gly	Pro	Gly	Lys	Arg	Arg	Gly	Val	Ala	Thr	Pro	Val Ile
			660					665					670	
Phe	Ala	Gly	Thr	Ser	Gly	Cys	Gly	Val	Gly	Asn	Leu	Thr	Glu	Pro Val
	675						680					685		
Ala	Val	Ser	Leu	Arg	His	Trp	Ala	Glu	Gly	Ala	Glu	Pro	Val	Ala Ala
	690					695					700			
Trp	Trp	Ser	Gln	Glu	Gly	Pro	Gly	Glu	Ala	Gly	Gly	Trp	Thr	Ser Glu
705					710					715				720

Gly Cys Gln Leu Arg Ser Ser Gln Pro Asn Val Ser Ala Leu His Cys
 725 730 735
 Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
 740 745 750
 Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
 755 760 765
 Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
 770 775 780
 Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
 785 790 795 800
 Leu Leu Asn Leu Cys Phe His Ile Ala Met Thr Ser Ala Val Phe Ala
 805 810 815
 Gly Gly Ile Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly
 820 825 830
 Ile Thr Leu His Tyr Ser Ser Leu Ser Thr Leu Leu Trp Met Gly Val
 835 840 845
 Lys Ala Arg Val Leu His Lys Glu Leu Thr Trp Arg Ala Pro Pro Pro
 850 855 860
 Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe
 865 870 875 880
 Tyr Leu Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala
 885 890 895
 Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu
 900 905 910
 Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile
 915 920 925
 Leu Leu Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu Arg Leu Arg
 930 935 940
 Gly Pro Leu Ala Gln Asn Pro Lys Ala Gly Asn Ser Arg Ala Ser Leu
 945 950 955 960
 Glu Ala Gly Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Gly Ser Gly
 965 970 975
 Pro Leu Leu Ser Asp Ser Gly Ser Leu Leu Ala Thr Gly Ser Ala Arg
 980 985 990
 Val Gly Thr Pro Gly Pro Pro Glu Asp Gly Asp Ser Leu Tyr Ser Pro
 995 1000 1005
 Gly Val Gln Leu Gly Ala Leu Val Thr Thr His Phe Leu Tyr Leu Ala
 1010 1015 1020
 Met Trp Ala Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg
 1025 1030 1035 1040
 Val Val Cys Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu
 1045 1050 1055
 Phe Val Phe Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser
 1060 1065 1070
 Trp Arg Ala Cys Cys Pro Pro Ala Ser Pro Ala Ala Pro His Ala Pro
 1075 1080 1085
 Pro Arg Ala Leu Pro Ala Ala Ala Glu Asp Gly Ser Pro Val Phe Gly
 1090 1095 1100
 Glu Gly Pro Pro Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly His
 1105 1110 1115 1120
 Pro Leu Ala Leu Gly Pro Cys Lys Leu Thr Asn Leu Gln Leu Ala Gln
 1125 1130 1135
 Ser Gln Val Cys Glu Ala Gly Ala Ala Gly Gly Glu Gly Glu Pro
 1140 1145 1150
 Glu Pro Ala Gly Thr Arg Gly Asn Leu Ala His Arg His Pro Asn Asn
 1155 1160 1165
 Val His His Gly Arg Arg Ala His Lys Ser Arg Ala Lys Gly His Arg
 1170 1175 1180
 Ala Gly Glu Ala Cys Gly Lys Asn Arg Leu Lys Ala Leu Arg Gly Gly
 1185 1190 1195 1200
 Ala Ala Gly Ala Leu Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His

1205								1210				1215			
Asn	Ser	Pro	Thr	Asp	Ser	Tyr	Leu	Gly	Ser	Ser	Arg	Asn	Ser	Pro	Gly
1220								1225				1230			
Ala	Gly	Leu	Gln	Leu	Glu	Gly	Glu	Pro	Met	Leu	Thr	Pro	Ser	Glu	Gly
1235								1240				1245			
Ser	Asp	Thr	Ser	Ala	Ala	Pro	Leu	Ser	Glu	Ala	Gly	Arg	Ala	Gly	Gln
1250								1255				1260			
Arg	Arg	Ser	Ala	Ser	Arg	Asp	Ser	Leu	Lys	Gly	Gly	Gly	Ala	Leu	Glu
1265								1270				1275			
Lys	Glu	Ser	His	Arg	Arg	Ser	Tyr	Pro	Leu	Asn	Ala	Ala	Ser	Leu	Asn
1285								1290				1295			
Gly	Ala	Pro	Lys	Gly	Gly	Lys	Tyr	Asp	Asp	Val	Thr	Leu	Met	Gly	Ala
1300								1305				1310			
Glu	Val	Ala	Ser	Gly	Gly	Cys	Met	Lys	Thr	Gly	Leu	Trp	Lys	Ser	Glu
1315								1320				1325			
Thr	Thr	Val													
1330															

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<210> 189
<211> 529
<212> PRT
<213> Homo sapiens
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	<400> 189														
Met 1	Ala	Arg	Phe	Pro 5	Lys	Ala	Asp	Leu	Ala 10	Ala	Ala	Gly	Val	Met 15	Leu
Leu	Cys	His	Phe 20	Phe	Thr	Asp	Gln	Phe 25	Gln	Phe	Ala	Asp	Gly 30	Lys	Pro
Gly	Asp	Gln 35	Ile	Leu	Asp	Trp	Gln 40	Tyr	Gly	Val	Thr	Gln 45	Ala	Phe	Pro
His	Thr 50	Glu	Glu	Glu	Val	Glu 55	Val	Asp	Ser	His	Ala 60	Tyr	Ser	His	Arg
Trp 65	Lys	Arg	Asn	Leu	Asp 70	Phe	Leu	Lys	Ala	Val 75	Asp	Thr	Asn	Arg	Ala 80
Ser	Val	Gly	Gln 85	Asp	Ser	Pro	Glu	Pro	Arg 90	Ser	Phe	Thr	Asp	Leu 95	Leu
Leu	Asp	Asp	Gly 100	Gln	Asp	Asn	Asn	Thr 105	Gln	Ile	Glu	Glu	Asp 110	Thr	Asp
His	Asn 115	Tyr	Tyr	Ile	Ser	Arg	Ile 120	Tyr	Gly	Pro	Ser	Asp 125	Ser	Ala	Ser
Arg	Asp 130	Leu	Trp	Val	Asn 135	Ile	Asp	Gln	Met	Glu	Lys 140	Asp	Lys	Val	Lys
Ile 145	His	Gly	Ile	Leu	Ser 150	Asn	Thr	His	Arg	Gln 155	Ala	Ala	Arg	Val	Asn 160
Leu	Ser	Phe	Asp 165	Phe	Pro	Phe	Tyr	Gly	His 170	Phe	Leu	Arg	Glu	Ile 175	Thr
Val	Ala	Thr 180	Gly	Phe	Ile	Tyr	Thr 185	Gly	Glu	Val	Val	His 190	Arg	Met	
Leu	Thr 195	Ala	Thr	Gln	Tyr	Ile	Ala 200	Pro	Leu	Met	Ala	Asn 205	Phe	Asp	Pro
Ser	Val 210	Ser	Arg	Asn	Ser	Thr 215	Val	Arg	Tyr	Phe	Asp 220	Asn	Gly	Thr	Ala
Leu 225	Val	Val	Gln	Trp	Asp 230	His	Val	His	Leu	Gln	Asp 235	Asn	Tyr	Asn	Leu 240
Gly	Ser	Phe	Thr 245	Phe	Gln	Ala	Thr	Leu	Leu 250	Met	Asp	Gly	Arg	Ile 255	Ile
Phe	Gly	Tyr 260	Lys	Glu	Ile	Pro	Val 265	Leu	Val	Thr	Gln	Ile	Ser 270	Ser	Thr
Asn	His 275	Pro	Val	Lys	Val	Gly	Leu 280	Ser	Asp	Ala	Phe	Val 285	Val	Val	His
Arg	Ile	Gln	Gln	Ile	Pro	Asn	Val	Arg	Arg	Arg	Thr	Ile	Tyr	Glu	Tyr

290 295 300
 His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
 305 310 315 320
 Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
 325 330 335
 Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
 340 345 350
 Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
 355 360 365
 Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
 370 375 380
 Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
 385 390 395 400
 Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
 405 410 415
 Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
 420 425 430
 Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
 435 440 445
 Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
 450 455 460
 Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
 465 470 475 480
 Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
 485 490 495
 Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
 500 505 510
 Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu Gln
 515 520 525
 Cys

<210> 190
 <211> 765
 <212> PRT
 <213> Mus musculus

<400> 190
 Met Leu Leu Arg Leu Leu Leu Ala Trp Val Ala Ala Val Pro Ala Leu
 1 5 10 15
 Gly Gln Val Pro Trp Thr Pro Glu Pro Arg Ala Ala Cys Gly Pro Ser
 20 25 30
 Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
 35 40 45
 Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
 50 55 60
 Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
 65 70 75 80
 Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
 85 90 95
 Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
 100 105 110
 Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
 115 120 125
 Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
 130 135 140
 Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
 145 150 155 160
 Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
 165 170 175
 Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp

48

Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser
 675 680 685
 Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys
 690 695 700
 Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg
 705 710 715 720
 Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp
 725 730 735
 Val Thr His Ala Gly Asn Lys Ser Ser Thr Glu Pro Met Pro Pro Arg
 740 745 750
 Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr Ser Val
 755 760 765

<210> 191
 <211> 1329
 <212> PRT
 <213> Mus musculus

<400> 191
 Met Pro Val Pro Pro Ala Arg Leu Leu Leu Leu Pro Leu Leu Pro Cys
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 Leu Leu Leu Leu Ala Pro Gly Thr Arg Gly Ala Pro Gly Cys Pro Val
 20 25 30
 Pro Ile Arg Gly Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
 35 40 45
 Gly Gly Ala His Asn Pro Ala Arg Arg Arg Val Val Cys Gly Gly Gly
 50 55 60
 Asp Leu Pro Glu Pro Pro Asp Pro Gly Leu Leu Pro Asn Gly Thr Ile
 65 70 75 80
 Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
 85 90 95
 Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Ser Asn Val
 100 105 110
 Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
 115 120 125
 Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
 130 135 140
 Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
 145 150 155 160
 Tyr Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
 165 170 175
 Ile Val Asp Phe Gly Thr Glu Phe Leu Thr Cys Asp Cys Arg Leu Arg
 180 185 190
 Trp Leu Leu Pro Trp Ala Arg Asn His Ser Leu Gln Leu Ser Glu Arg
 195 200 205
 Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala His Ala Leu Ser Ser
 210 215 220
 Leu Gln Glu Ser Gln Leu Arg Cys Glu Gly Ala Leu Glu Leu His Thr
 225 230 235 240
 His Tyr Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
 245 250 255
 Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
 260 265 270
 His Trp Tyr His Asn Gly Ala Pro Met Glu Ser Asp Glu Gln Ala Gly
 275 280 285
 Ile Val Leu Ala Glu Asn Leu Ile His Asp Cys Thr Phe Ile Thr Ser
 290 295 300
 Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
 305 310 315 320
 Cys Ser Val Ser Thr Val Gln Gly Asn Thr Ser Lys Lys Val Glu Ile
 325 330 335

Val	Val	Leu	Glu	Thr	Ser	Ala	Ser	Tyr	Cys	Pro	Ala	Glu	Arg	Val	Thr
			340					345					350		
Asn	Asn	Arg	Gly	Asp	Phe	Arg	Trp	Pro	Arg	Thr	Leu	Ala	Gly	Ile	Thr
		355					360					365			
Ala	Tyr	Gln	Ser	Cys	Leu	Gln	Tyr	Pro	Phe	Thr	Ser	Val	Pro	Leu	Ser
	370					375					380				
Gly	Gly	Ala	Pro	Gly	Thr	Arg	Ala	Ser	Arg	Arg	Cys	Asp	Arg	Ala	Gly
385					390					395					400
Arg	Trp	Glu	Pro	Gly	Asp	Tyr	Ser	His	Cys	Leu	Tyr	Thr	Asn	Asp	Ile
				405					410					415	
Thr	Arg	Val	Leu	Tyr	Thr	Phe	Val	Leu	Met	Pro	Ile	Asn	Ala	Ser	Asn
			420					425					430		
Ala	Leu	Thr	Leu	Ala	His	Gln	Leu	Arg	Val	Tyr	Thr	Ala	Glu	Ala	Ala
		435					440					445			
Ser	Phe	Ser	Asp	Met	Met	Asp	Val	Val	Tyr	Val	Ala	Gln	Met	Ile	Gln
	450					455					460				
Lys	Phe	Leu	Gly	Tyr	Val	Asp	Gln	Ile	Lys	Glu	Leu	Val	Glu	Val	Met
465					470					475					480
Val	Asp	Met	Ala	Ser	Asn	Leu	Met	Leu	Val	Asp	Glu	His	Leu	Leu	Trp
				485					490					495	
Leu	Ala	Gln	Arg	Glu	Asp	Lys	Ala	Cys	Ser	Gly	Ile	Val	Gly	Ala	Leu
		500						505					510		
Glu	Arg	Ile	Gly	Gly	Ala	Ala	Leu	Ser	Pro	His	Ala	Gln	His	Ile	Ser
		515					520					525			
Val	Asn	Ser	Arg	Asn	Val	Ala	Leu	Glu	Ala	Tyr	Leu	Ile	Lys	Pro	His
	530					535					540				
Ser	Tyr	Val	Gly	Leu	Thr	Cys	Thr	Ala	Phe	Gln	Arg	Arg	Glu	Val	Gly
545					550					555					560
Val	Ser	Gly	Ala	Gln	Pro	Ser	Ser	Val	Gly	Gln	Asp	Ala	Pro	Val	Glu
			565						570					575	
Pro	Glu	Pro	Leu	Ala	Asp	Gln	Gln	Leu	Arg	Phe	Arg	Cys	Thr	Thr	Gly
			580					585					590		
Arg	Pro	Asn	Ile	Ser	Leu	Ser	Ser	Phe	His	Ile	Lys	Asn	Ser	Val	Ala
		595					600					605			
Leu	Ala	Ser	Ile	Gln	Leu	Pro	Pro	Ser	Leu	Phe	Ser	Thr	Leu	Pro	Ala
	610					615						620			
Ala	Leu	Ala	Pro	Pro	Val	Pro	Pro	Asp	Cys	Thr	Leu	Gln	Leu	Leu	Val
625					630					635					640
Phe	Arg	Asn	Gly	Arg	Leu	Phe	Arg	Ser	His	Gly	Asn	Asn	Thr	Ser	Arg
			645						650					655	
Pro	Gly	Ala	Ala	Gly	Pro	Gly	Lys	Arg	Arg	Gly	Val	Ala	Thr	Pro	Val
		660						665					670		
Ile	Phe	Ala	Gly	Thr	Ser	Gly	Cys	Gly	Val	Gly	Asn	Leu	Thr	Glu	Pro
		675					680					685			
Val	Ala	Val	Ser	Leu	Arg	His	Trp	Ala	Glu	Gly	Ala	Asp	Pro	Met	Ala
	690					695						700			
Ala	Trp	Trp	Asn	Gln	Asp	Gly	Pro	Gly	Gly	Trp	Ser	Ser	Glu	Gly	Cys
705				710						715					720
Arg	Leu	Arg	Tyr	Ser	Gln	Pro	Asn	Val	Ser	Ser	Leu	Tyr	Cys	Gln	His
			725						730					735	
Leu	Gly	Asn	Val	Ala	Val	Leu	Met	Glu	Leu	Asn	Ala	Phe	Pro	Arg	Glu
			740					745					750		
Ala	Gly	Gly	Ser	Gly	Ala	Gly	Leu	His	Pro	Val	Val	Tyr	Pro	Cys	Thr
		755					760					765			
Ala	Leu	Leu	Leu	Leu	Cys	Leu	Phe	Ser	Thr	Ile	Ile	Thr	Tyr	Ile	Leu
	770					775						780			
Asn	His	Ser	Ser	Ile	His	Val	Ser	Arg	Lys	Gly	Trp	His	Met	Leu	Leu
785					790					795					800
Asn	Leu	Cys	Phe	His	Met	Ala	Met	Thr	Ser	Ala	Val	Phe	Val	Gly	Gly
			805						810					815	
Val	Thr	Leu	Thr	Asn	Tyr	Gln	Met	Val	Cys	Gln	Ala	Val	Gly	Ile	Thr

										820			825				830			
Leu	His	Tyr	Ser	Ser	Leu	Ser	Ser	Leu	Leu	Trp	Met	Gly	Val	Lys	Ala					
		835					840					845								
Arg	Val	Leu	His	Lys	Glu	Leu	Ser	Trp	Arg	Ala	Pro	Pro	Leu	Glu	Glu					
		850					855					860								
Gly	Glu	Ala	Ala	Pro	Pro	Gly	Pro	Arg	Pro	Met	Leu	Arg	Phe	Tyr	Leu					
865							870					875								
Ile	Ala	Gly	Gly	Ile	Pro	Leu	Ile	Ile	Cys	Gly	Ile	Thr	Ala	Ala	Val					
Asn	Ile	His	Asn	Tyr	Arg	Asp	His	Ser	Pro	Tyr	Cys	Trp	Leu	Val	Trp					
Arg	Pro	Ser	Leu	Gly	Ala	Phe	Tyr	Ile	Pro	Val	Ala	Leu	Ile	Leu	Pro					
Ile	Thr	Trp	Ile	Tyr	Phe	Leu	Cys	Ala	Gly	Leu	His	Leu	Arg	Ser	His					
Val	Ala	Gln	Asn	Pro	Lys	Gln	Gly	Asn	Arg	Ile	Ser	Leu	Glu	Pro	Gly					
945							950					955								
Glu	Glu	Leu	Arg	Gly	Ser	Thr	Arg	Leu	Arg	Ser	Ser	Gly	Val	Leu	Leu					
Asn	Asp	Ser	Gly	Ser	Leu	Leu	Ala	Thr	Val	Ser	Ala	Gly	Val	Gly	Thr					
Pro	Ala	Pro	Pro	Glu	Asp	Gly	Asp	Gly	Val	Tyr	Ser	Pro	Gly	Val	Gln					
Leu	Gly	Ala	Leu	Met	Thr	Thr	His	Phe	Leu	Tyr	Leu	Ala	Met	Trp	Ala					
Cys	Gly	Ala	Leu	Ala	Val	Ser	Gln	Arg	Trp	Leu	Pro	Arg	Val	Val	Cys					
1025							1030					1035								
Ser	Cys	Leu	Tyr	Gly	Val	Ala	Ala	Ser	Ala	Leu	Gly	Leu	Phe	Val	Phe					
Thr	His	His	Cys	Ala	Arg	Arg	Arg	Asp	Val	Arg	Ala	Ser	Trp	Arg	Ala					
Cys	Cys	Pro	Pro	Ala	Ser	Pro	Ser	Ala	Ser	His	Val	Pro	Ala	Arg	Ala					
Leu	Pro	Thr	Ala	Thr	Glu	Asp	Gly	Ser	Pro	Val	Leu									

Ile Ala Gly Gly Ser Met Lys Thr Gly Leu Trp Lys Ser Glu Thr Thr
 1315 1320 1325
 Val

<210> 192
 <211> 500
 <212> PRT
 <213> Mus musculus

<400> 192
 Met Arg Ala Gln Leu Trp Leu Leu Gln Leu Leu Leu Leu Arg Gly Ala
 1 5 10 15
 Ala Arg Ala Leu Ser Pro Ala Thr Pro Ala Gly His Asn Glu Gly Gln
 20 25 30
 Asp Ser Ala Trp Thr Ala Lys Arg Thr Arg Gln Gly Trp Ser Arg Arg
 35 40 45
 Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
 50 55 60
 Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
 65 70 75 80
 Asn Arg Thr Arg Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
 85 90 95
 Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
 100 105 110
 Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
 115 120 125
 Ser His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe
 130 135 140
 Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
 145 150 155 160
 Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
 165 170 175
 Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
 180 185 190
 Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
 195 200 205
 Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala
 210 215 220
 Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro
 225 230 235 240
 Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly
 245 250 255
 Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu
 260 265 270
 Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
 275 280 285
 Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
 290 295 300
 Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
 305 310 315 320
 Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe
 325 330 335
 Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala
 340 345 350
 Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala
 355 360 365
 Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser
 370 375 380
 Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu
 385 390 395 400

Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
 405 410 415
 Ser Lys Gly Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
 420 425 430
 Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
 435 440 445
 Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
 450 455 460
 His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr
 465 470 475 480
 Tyr Thr Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe Val Glu
 485 490 495
 Ala Glu Gln Cys
 500

<210> 193
 <211> 530
 <212> PRT
 <213> Mus musculus

<400> 193
 Met Ala Arg Phe Arg Arg Ala Asp Leu Ala Ala Ala Gly Val Met Leu
 1 5 10 15
 Leu Cys His Phe Leu Thr Asp Arg Phe His Phe Ala His Gly Glu Pro
 20 25 30
 Gly His His Thr Asn Asp Trp Ile Tyr Glu Val Thr Asn Ala Phe Pro
 35 40 45
 Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
 50 55 60
 Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
 65 70 75 80
 Ser Met Gly Gln Ala Ser Pro Glu Ser Lys Gly Phe Thr Asp Leu Leu
 85 90 95
 Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
 100 105 110
 His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
 115 120 125
 Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
 130 135 140
 Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
 145 150 155 160
 Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
 165 170 175
 Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
 180 185 190
 Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
 195 200 205
 Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
 210 215 220
 Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
 225 230 235 240
 Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
 245 250 255
 Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
 260 265 270
 Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
 275 280 285
 Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
 290 295 300
 His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
 305 310 315 320

Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Gly Cys Gly Pro
 325 330 335
 Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
 340 345 350
 Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
 355 360 365
 Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys
 370 375 380
 Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Ser His Thr Thr
 385 390 395 400
 Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser
 405 410 415
 Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu
 420 425 430
 His Leu Lys Asp Ser Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys
 435 440 445
 Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu
 450 455 460
 Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His
 465 470 475 480
 His Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser
 485 490 495
 Arg Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr
 500 505 510
 Ala Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu
 515 520 525
 Gln Cys
 530

<210> 194
 <211> 562
 <212> PRT
 <213> Mus musculus

<400> 194
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 Ala Ala Leu Val Leu Val Cys Ala Gly His Gly Gly Arg Arg Glu Asp
 20 25 30
 Gly Gly Pro Ala Cys Tyr Gly Gly Phe Asp Leu Tyr Phe Ile Leu Asp
 35 40 45
 Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
 50 55 60
 Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
 65 70 75 80
 Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
 85 90 95
 Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
 100 105 110
 Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
 115 120 125
 Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
 130 135 140
 Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
 145 150 155 160
 Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
 165 170 175
 Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
 180 185 190
 Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
 195 200 205

Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
 210 215 220
 Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
 225 230 235 240
 Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
 245 250 255
 Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
 260 265 270
 Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
 275 280 285
 Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
 290 295 300
 Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
 305 310 315 320
 Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
 325 330 335
 Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
 340 345 350
 Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Asp Gly Leu
 355 360 365
 Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
 370 375 380
 Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
 385 390 395 400
 Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
 405 410 415
 Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
 420 425 430
 Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
 435 440 445
 Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
 450 455 460
 Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
 465 470 475 480
 Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
 485 490 495
 Asn Thr Tyr His Pro Ser Ser Pro Pro Pro Ala Pro Ile Tyr Thr Pro
 500 505 510
 Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
 515 520 525
 Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro Gln Ala
 530 535 540
 Pro Pro Pro Asn Arg Ala Pro Pro Pro Ser Arg Pro Pro Pro Arg Pro
 545 550 555 560
 Ser Val

<210> 195
 <211> 2565
 <212> DNA
 <213> Homo sapiens

<400> 195
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 acccctgggc tgctgagccc cgtgccgcct gcgggcccag cagctgctac gctctcttcc 120
 cacggcgccg caccttctctg gaggcctggc gggcctgccg cgagctgggg ggcgacctgg 180
 ccactcctcg gacccccgag gagggccagc gtgtggacag cctggtgggt gcgggcccag 240
 ccagccggct gctgtggatc gggctgcagc ggcaggcccg gcaatgccag ctgcagcgcc 300
 cactgcgcgg cttcacgtgg accacagggg accaggacac ggctttcacc aactgggccc 360
 agccagcctc tggaggcccc tgcccggccc agcgctgtgt ggccctggag gcaagtggcg 420
 agcaccgctg gctggagggc tcgtgcacgc tggctgtcga cggctacctg tgccagtttg 480

gcttcgaggg	cgccctgccc	gcgctgcaag	atgaggcggg	ccaggccggc	ccagccgtgt	540
ataccacgcc	cttccacctg	gtctccacag	agtttgagt	gctgcccttc	ggctctgtgg	600
ccgctgtgca	gtgccaggct	ggcaggggag	cctctctgct	ctgcgtgaag	cagcctgagg	660
gaggtgtggg	ctgggtcacgg	gctggggccc	tgtgcctggg	gactggctgc	agccctgaca	720
acgggggctg	cgaacacgaa	tgtgtggagg	aggtggatgg	tcacgtgtcc	tgccgctgca	780
ctgagggctt	ccggctggca	gcagacgggc	gcagttgcga	ggaccctgt	gcccaggctc	840
cgtgcgagca	gcagtgtgag	cccgggtggc	cacaaggcta	cagctgccac	tgctgcctgg	900
gtttccggcc	agcggaggat	gatccgcacc	gctgtgtgga	cacagatgag	tgccagattg	960
ccggtgtgtg	ccagcagatg	tgtgtcaact	acgttggtgg	cttcgagtgt	tattgtagcg	1020
agggacatga	gctggaggct	gatggcatca	gctgcagccc	tgacggggcc	atgggtgccc	1080
aggcttccca	ggacctcgga	gatgagttgc	tggtatgacg	ggaggtgag	gaagatgaag	1140
acgaggcctg	gaaggccttc	aacgggtggc	ggacggagat	gcctgggatc	ctgtggatgg	1200
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agccacagat	accctaccgg	gagcccacct	ggccaccccc	gctcagtgcc	cccagggtcc	1320
cctaccactc	ctcagtgtct	tccgtcaccc	ggcctgtggt	ggtctctgcc	acgcattcca	1380
cactgccttc	tgcccaccag	cctcctgtga	tccctgccac	acaccagct	ttgtcccgtg	1440
accaccagat	cccctgtatc	gcagccaact	atccagatcc	gccttctgcc	taccaaccgg	1500
gtattctctc	tgtctctcat	tcagcacagc	ctcctgcccc	ccagccccct	atgatctcaa	1560
ccaaatatcc	ggagctcttc	cctgcccacc	agtcccccat	gtttccagac	acccgggtcg	1620
ctggcaccca	gaccaccact	catttgcttg	gaatcccacc	taaccatgcc	cctctggtca	1680
ccaccctcgg	tgcccagcta	ccccctcaag	ccccagatgc	ccttgtcctc	agaacccagg	1740
ccaccagct	tcccattatc	ccaactgccc	agccctctct	gaccaccacc	tccagggtccc	1800
ctgtgtctcc	tgcccattcaa	atctctgtgc	ctgctgccac	ccagcccgca	gccctcccca	1860
ccctcctgcc	ctctcagagc	cccactaacc	agacctcacc	catcagccct	acacctcccc	1920
attccaaagc	cccccaaatt	ccaagggaag	atggccccag	tcccaagttg	gccctgtggc	1980
tgccctcacc	agctcccaca	gcagcccca	cagccctggg	ggaggtctgt	cttgccgagc	2040
acagccagag	ggatgaccgg	tggtgtctgg	tggtactcct	ggtgccaacg	tgtgtctttt	2100
tggtggtcct	gcttgactgc	ggcatcgtgt	actgcacccg	ctgtggcccc	catgcacca	2160
acaagcgcat	cactgactgc	tatcgctggg	tcatccatgc	tgggagcaag	agcccaacag	2220
aacctatgcc	ccccaggggc	agcctcacag	gggtgcagac	ctgcagaacc	agcgtgtgat	2280
ggggtgcaga	ccccctcat	ggagtatggg	gcgctggaca	catggccggg	gctgcaccag	2340
ggacccatgg	gggtgtgcca	gctggacaga	tggcttcctg	ctccccaggc	ccagccaggg	2400
tcctctctca	accactagac	ttggctctca	ggaaactctg	ttcctggccc	agcgtcctgt	2460
accaaggata	caccaagcc	cttaagacct	cagggggcgg	gtgctggggg	cttctccaat	2520
aaatgggggt	tcaaccttaa	aaaaaaaaaa	aaaaaaaaaa	aaaaa		2565

<210> 196

<211> 757

<212> PRT

<213> Homo sapiens

<400> 196

Met	Leu	Leu	Arg	Leu	Leu	Leu	Ala	Trp	Ala	Ala	Ala	Gly	Pro	Thr	Leu
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Gly	Gln	Asp	Pro	Trp	Ala	Ala	Glu	Pro	Arg	Ala	Ala	Cys	Gly	Pro	Ser
			20					25					30		
Ser	Cys	Tyr	Ala	Leu	Phe	Pro	Arg	Arg	Arg	Thr	Phe	Leu	Glu	Ala	Trp
		35					40					45			
Arg	Ala	Cys	Arg	Glu	Leu	Gly	Gly	Asp	Leu	Ala	Thr	Pro	Arg	Thr	Pro
	50					55					60				
Glu	Glu	Ala	Gln	Arg	Val	Asp	Ser	Leu	Val	Gly	Ala	Gly	Pro	Ala	Ser
	65				70					75					80
Arg	Leu	Leu	Trp	Ile	Gly	Leu	Gln	Arg	Gln	Ala	Arg	Gln	Cys	Gln	Leu
				85					90					95	
Gln	Arg	Pro	Leu	Arg	Gly	Phe	Thr	Trp	Thr	Thr	Gly	Asp	Gln	Asp	Thr
			100					105					110		
Ala	Phe	Thr	Asn	Trp	Ala	Gln	Pro	Ala	Ser	Gly	Gly	Pro	Cys	Pro	Ala
	115						120					125			
Gln	Arg	Cys	Val	Ala	Leu	Glu	Ala	Ser	Gly	Glu	His	Arg	Trp	Leu	Glu
	130					135					140				
Gly	Ser	Cys	Thr	Leu	Ala	Val	Asp	Gly	Tyr	Leu	Cys	Gln	Phe	Gly	Phe

145					150					155				160
Glu	Gly	Ala	Cys	Pro	Ala	Leu	Gln	Asp	Glu	Ala	Gly	Gln	Ala	Gly
				165					170					175
Ala	Val	Tyr	Thr	Thr	Pro	Phe	His	Leu	Val	Ser	Thr	Glu	Phe	Glu
			180					185					190	
Leu	Pro	Phe	Gly	Ser	Val	Ala	Ala	Val	Gln	Cys	Gln	Ala	Gly	Arg
		195					200					205		
Ala	Ser	Leu	Leu	Cys	Val	Lys	Gln	Pro	Glu	Gly	Gly	Val	Gly	Trp
	210					215					220			Ser
Arg	Ala	Gly	Pro	Leu	Cys	Leu	Gly	Thr	Gly	Cys	Ser	Pro	Asp	Asn
225					230					235				240
Gly	Cys	Glu	His	Glu	Cys	Val	Glu	Glu	Val	Asp	Gly	His	Val	Ser
				245				250						255
Arg	Cys	Thr	Glu	Gly	Phe	Arg	Leu	Ala	Ala	Asp	Gly	Arg	Ser	Cys
		260						265					270	Glu
Asp	Pro	Cys	Ala	Gln	Ala	Pro	Cys	Glu	Gln	Gln	Cys	Glu	Pro	Gly
	275						280					285		Gly
Pro	Gln	Gly	Tyr	Ser	Cys	His	Cys	Arg	Leu	Gly	Phe	Arg	Pro	Ala
	290					295					300			Glu
Asp	Asp	Pro	His	Arg	Cys	Val	Asp	Thr	Asp	Glu	Cys	Gln	Ile	Ala
305					310					315				320
Val	Cys	Gln	Gln	Met	Cys	Val	Asn	Tyr	Val	Gly	Gly	Phe	Glu	Cys
				325					330					335
Cys	Ser	Glu	Gly	His	Glu	Leu	Glu	Ala	Asp	Gly	Ile	Ser	Cys	Ser
		340						345					350	Pro
Ala	Gly	Ala	Met	Gly	Ala	Gln	Ala	Ser	Gln	Asp	Leu	Gly	Asp	Glu
	355						360					365		Leu
Leu	Asp	Asp	Gly	Glu	Asp	Glu	Glu	Asp	Glu	Asp	Glu	Ala	Trp	Lys
	370					375					380			Ala
Phe	Asn	Gly	Gly	Trp	Thr	Glu	Met	Pro	Gly	Ile	Leu	Trp	Met	Glu
385					390					395				400
Thr	Gln	Pro	Pro	Asp	Phe	Ala	Leu	Ala	Tyr	Arg	Pro	Ser	Phe	Pro
				405					410					415
Asp	Arg	Glu	Pro	Gln	Ile	Pro	Tyr	Pro	Glu	Pro	Thr	Trp	Pro	Pro
		420						425					430	Pro
Leu	Ser	Ala	Pro	Arg	Val	Pro	Tyr	His	Ser	Ser	Val	Leu	Ser	Val
	435						440					445		Thr
Arg	Pro	Val	Val	Val	Ser	Ala	Thr	His	Pro	Thr	Leu	Pro	Ser	Ala
	450					455					460			His
Gln	Pro	Pro	Val	Ile	Pro	Ala	Thr	His	Pro	Ala	Leu	Ser	Arg	Asp
465					470					475				480
Gln	Ile	Pro	Val	Ile	Ala	Ala	Asn	Tyr	Pro	Asp	Leu	Pro	Ser	Ala
				485					490					495
Gln	Pro	Gly	Ile	Leu	Ser	Val	Ser	His	Ser	Ala	Gln	Pro	Pro	Ala
		500						505					510	His
Gln	Pro	Pro	Met	Ile	Ser	Thr	Lys	Tyr	Pro	Glu	Leu	Phe	Pro	Ala
	515						520					525		His
Gln	Ser	Pro	Met	Phe	Pro	Asp	Thr	Arg	Val	Ala	Gly	Thr	Gln	Thr
	530					535					540			Thr
Thr	His	Leu	Pro	Gly	Ile	Pro	Pro	Asn	His	Ala	Pro	Leu	Val	Thr
545					550					555				560
Leu	Gly	Ala	Gln	Leu	Pro	Pro	Gln	Ala	Pro	Asp	Ala	Leu	Val	Leu
				565				570						575
Thr	Gln	Ala	Thr	Gln	Leu	Pro	Ile	Ile	Pro	Thr	Ala	Gln	Pro	Ser
			580					585					590	Leu
Thr	Thr	Thr	Ser	Arg	Ser	Pro	Val	Ser	Pro	Ala	His	Gln	Ile	Ser
		595					600					605		Val
Pro	Ala	Ala	Thr	Gln	Pro	Ala	Ala	Leu	Pro	Thr	Leu	Leu	Pro	Ser
	610					615					620			Gln
Ser	Pro	Thr	Asn	Gln	Thr	Ser	Pro	Ile	Ser	Pro	Thr	His	Pro	His
625					630					635				640

Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
 645 650 655
 Leu Trp Leu Pro Ser Pro Ala Pro Thr Ala Ala Pro Thr Ala Leu Gly
 660 665 670
 Glu Ala Gly Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu
 675 680 685
 Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
 690 695 700
 Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
 705 710 715 720
 Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
 725 730 735
 Pro Thr Glu Pro Met Pro Pro Arg Gly Ser Leu Thr Gly Val Gln Thr
 740 745 750
 Cys Arg Thr Ser Val
 755

<210> 197
 <211> 2973
 <212> DNA
 <213> Homo sapiens

<400> 197
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 gatccccgcg cagtgacccg ggagccacca cagactctgg gaggtcggc ggctggagca 120
 gcaggcagct cccgcagct cccggcgctt ccaggcagct ctctgagccg tgccagaggc 180
 ccggccccgc attcccagcc ccgagccatg atgaagactt tgtccagcgg gaactgcacg 240
 ctcaagtgtgc ccgcaaaaa ctcataccgc atgggtgggtg tgggtgcctc tcgggtgggc 300
 aagagctcca tcgtgtctcg cttcctcaat ggccgctttg aggaccagta cacaccacc 360
 atcgaggact tccaccgtaa ggtatacaac atccgcggcg acatgtacca gctcgacatc 420
 ctggatacct ctggcaacca ccccttcccc gccatggcga ggctgtccat cctcacaggg 480
 gatgtcttca tcctgggtgtt cagcgtgaat aaccgggagt ccttcgatga ggtcaagcgc 540
 cttcagaagc agatcctgga ggtcaagtcc tgctgaaga acaagaccaa ggaggcggcg 600
 gagctgcccc tgggtcatctg tggcaacaag aacgaccacg gcgagctgtg ccgccagggtg 660
 cccaccaccg agggcgagct gctgggtgtc ggcgacgaga actgcgccta cttcgagggtg 720
 tcggccaaga agaacaccaa cgtggacgag atgttctacg tgctcttcag catggccaag 780
 ctgccacacg agatgagccc cgccctgcat cgcaagatct ccgtgcagta cggtagcggc 840
 ttccacccca ggcccttctg catgcgccgc gtcaaggaga tggacgccta tggcatggtc 900
 tcgcccttcg cccgcgcgcc cagcgtcaac agtgacctca agtacatcaa ggccaaggtc 960
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<210> 198
 <211> 266
 <212> PRT
 <213> Homo sapiens

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35      40      45
Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly
50      55      60
Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
65      70      75      80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
85      90      95
Val Phe Ser Leu Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
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Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
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Gly Glu Leu Cys Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val
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Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
165     170     175
Thr Asn Val Asp Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
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Pro His Glu Met Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr
195     200     205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu
210     215     220
Met Asp Ala Tyr Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val
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 <212> DNA
 <213> Homo sapiens

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<210> 200

<211> 529

<212> PRT

<213> Homo sapiens

<400> 200

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			20					25					30	Pro
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		35					40					45		Pro
His	Thr	Glu	Glu	Glu	Val	Glu	Val	Asp	Ser	His	Ala	Tyr	Ser	His
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Trp	Lys	Arg	Asn	Leu	Asp	Phe	Leu	Lys	Ala	Val	Asp	Thr	Asn	Arg
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Leu	Asp	Asp	Gly	Gln	Asp	Asn	Asn	Thr	Gln	Ile	Glu	Glu	Asp	Thr
			100					105					110	Asp
His	Asn	Tyr	Tyr	Ile	Ser	Arg	Ile	Tyr	Gly	Pro	Ser	Asp	Ser	Ala
		115					120					125		Ser
Arg	Asp	Leu	Trp	Val	Asn	Ile	Asp	Gln	Met	Glu	Lys	Asp	Lys	Val
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 180 185 190
 Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
 195 200 205
 Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
 210 215 220
 Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
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 245 250 255
 Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
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 Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
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 Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
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 Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
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 <212> DNA
 <213> Homo sapiens

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<210> 202

<211> 350

<212> PRT

<213> Homo sapiens

<400> 202

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Lys Pro Gly Pro Ala Leu Ser Tyr Pro Gln Glu Glu Ala Thr Leu Asn
35           40           45
Glu Met Phe Arg Glu Val Glu Glu Leu Met Glu Asp Thr Gln His Lys
50           55           60
Leu Arg Ser Ala Val Glu Glu Met Glu Ala Glu Glu Ala Ala Ala Lys
65           70           75           80
Ala Ser Ser Glu Val Asn Leu Ala Asn Leu Pro Pro Ser Tyr His Asn
85           90           95
Glu Thr Asn Thr Asp Thr Lys Val Gly Asn Asn Thr Ile His Val His
100          105          110
Arg Glu Ile His Lys Ile Thr Asn Asn Gln Thr Gly Gln Met Val Phe

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Phe	Ala Ser Phe Gln Tyr Thr	Cys Gln Pro Cys Arg	Gly Gln Arg Met		
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Leu	Cys Thr Arg Asp Ser	Glu Cys Cys Gly Asp	Gln Leu Cys Val Trp		
	180	185	190		
Gly	His Cys Thr Lys Met Ala	Thr Arg Gly Ser Asn	Gly Thr Ile Cys		
	195	200	205		
Asp	Asn Gln Arg Asp Cys	Gln Pro Gly Leu Cys	Cys Ala Phe Gln Arg		
210		215	220		
Gly	Leu Leu Phe Pro Val	Cys Thr Pro Leu Pro	Val Glu Gly Glu Leu		
225		230	235		240
Cys	His Asp Pro Ala Ser	Arg Leu Leu Asp Leu	Ile Thr Trp Glu Leu		
	245	250	255		
Glu	Pro Asp Gly Ala Leu	Asp Arg Cys Pro Cys	Ala Ser Gly Leu Leu		
	260	265	270		
Cys	Gln Pro His Ser His	Ser Leu Val Tyr Val	Cys Lys Pro Thr Phe		
	275	280	285		
Val	Gly Ser Arg Asp Gln	Asp Gly Glu Ile Leu	Leu Pro Arg Glu Val		
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Pro	Asp Glu Tyr Glu Val	Gly Ser Phe Met Glu	Glu Val Arg Gln Glu		
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Leu	Glu Asp Leu Glu Arg	Ser Leu Thr Glu Glu	Met Ala Leu Gly Glu		
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 <212> DNA
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<400> 203

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 50          55          60
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Ser Val Arg Gln Leu Ser Arg Arg Phe Asp Ala Pro Arg Leu Asp Asp
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1765	1770	1775
Ile Leu Tyr Leu Asn Asn Gln	Val Phe Val Ser Leu Ala	Asn Gly Glu
1780	1785	1790
Leu Val Val Tyr Gln Arg Glu	Ala Gly His Phe Trp Asp	Pro Gln Asn
1795	1800	1805
Phe Lys Ser Val Thr Leu Gly	Thr Gln Gly Ser Pro Ile	Thr Lys Met
1810	1815	1820
Val Ser Val Gly Gly Arg Leu	Trp Cys Gly Cys Gln Asn	Arg Val Leu
1825	1830	1835
Val Leu Ser Pro Asp Thr Leu	Gln Leu Glu His Met Phe	Tyr Val Gly
1845	1850	1855
Gln Asp Ser Ser Arg Cys Val	Ala Cys Met Val Asp Ser	Ser Ser Leu Gly
1860	1865	1870
Val Trp Val Thr Leu Lys Gly	Ser Ala His Val Cys Leu	Tyr His Pro
1875	1880	1885
Asp Thr Phe Glu Gln Leu Ala	Glu Val Asp Val Thr Pro	Pro Val His
1890	1895	1900
Arg Met Leu Ala Gly Ser Asp	Ala Ile Ile Arg Gln His	Lys Ala Ala
1905	1910	1915
Cys Leu Arg Ile Thr Ala Leu	Leu Val Cys Glu Glu Leu	Leu Trp Val
1925	1930	1935
Gly Thr Ser Ala Gly Val Val	Leu Thr Met Pro Thr Ser	Pro Gly Thr
1940	1945	1950
Val Ser Cys Pro Arg Ala Pro	Leu Ser Pro Thr Gly Leu	Gly Gln Gly
1955	1960	1965
His Thr Gly His Val Arg Phe	Leu Ala Ala Val Gln Leu	Pro Asp Gly
1970	1975	1980
Phe Asn Leu Leu Cys Pro Thr	Pro Pro Pro Pro Pro Asp	Thr Gly Pro
1985	1990	1995
Glu Lys Leu Pro Ser Leu Glu	His Arg Asp Ser Pro Trp	His Arg Gly
2005	2010	2015
Pro Ala Pro Ala Arg Pro Lys	Met Leu Val Ile Ser Gly	Gly Asp Gly
2020	2025	2030
Tyr Glu Asp Phe Arg Leu Ser	Ser Gly Gly Gly Ser Ser	Ser Ser Glu Thr
2035	2040	2045

Val Gly Arg Asp Asp Ser Thr Asn His Leu Leu Leu Trp Arg Val
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 <211> 2247
 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala

50	55	60
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65	70	75
Gly Val Pro Asp Pro Ser	Asp Gly Leu Ser	Ala Arg Asn Arg Gln Lys
	85	90
Arg Phe Val Leu Ser Gly	Gly Arg Trp Glu	Lys Thr Asp Leu Thr Tyr
	100	105
Arg Ile Leu Arg Phe Pro	Trp Gln Leu Val	Gln Glu Gln Val Arg Gln
	115	120
Thr Met Ala Glu Ala Leu	Lys Val Trp Ser	Asp Val Thr Pro Leu Thr
	130	135
Phe Thr Glu Val His Glu	Gly Arg Ala Asp	Ile Met Ile Asp Phe Ala
145	150	155
Arg Tyr Trp His Gly Asp	Asp Leu Pro Phe	Asp Gly Pro Gly Gly Ile
	165	170
Leu Ala His Ala Phe Phe	Pro Lys Thr His	Arg Glu Gly Asp Val His
	180	185
Phe Asp Tyr Asp Glu Thr	Trp Thr Ile Gly	Asp Asp Gln Gly Thr Asp
	195	200
Leu Leu Gln Val Ala Ala	His Glu Phe Gly	His Val Leu Gly Leu Gln
	210	215
His Thr Thr Ala Ala Lys	Ala Leu Met Ser	Ala Phe Tyr Thr Phe Arg
225	230	235
Tyr Pro Leu Ser Leu Ser	Pro Asp Asp Cys	Arg Gly Val Gln His Leu
	245	250
Tyr Gly Gln Pro Trp Pro	Thr Val Thr Ser	Arg Thr Pro Ala Leu Gly
	260	265
Pro Gln Ala Gly Ile Asp	Thr Asn Glu Ile	Ala Pro Leu Glu Pro Asp
	275	280
Ala Pro Pro Asp Ala Cys	Glu Ala Ser Phe	Asp Ala Val Ser Thr Ile
	290	295
Arg Gly Glu Leu Phe Phe	Phe Lys Ala Gly	Phe Val Trp Arg Leu Arg
305	310	315
Gly Gly Gln Leu Gln Pro	Gly Tyr Pro Ala	Leu Ala Ser Arg His Trp
	325	330
Gln Gly Leu Pro Ser Pro	Val Asp Ala Ala	Phe Glu Asp Ala Gln Gly
	340	345
His Ile Trp Phe Phe Gln	Gly Ala Gln Tyr	Trp Val Tyr Asp Gly Glu
	355	360
Lys Pro Val Leu Gly Pro	Ala Pro Leu Thr	Glu Leu Gly Leu Val Arg
	370	375
Phe Pro Val His Ala Ala	Leu Val Trp Gly	Pro Glu Lys Asn Lys Ile
385	390	395
Tyr Phe Phe Arg Gly Arg	Asp Tyr Trp Arg	Phe His Pro Ser Thr Arg
	405	410
Arg Val Asp Ser Pro Val	Pro Arg Arg Ala	Thr Asp Trp Arg Gly Val
	420	425
Pro Ser Glu Ile Asp Ala	Ala Phe Gln Asp	Ala Asp Gly Tyr Ala Tyr
	435	440
Phe Leu Arg Gly Arg Leu	Tyr Trp Lys Phe	Asp Pro Val Lys Val Lys
	450	455
Ala Leu Glu Gly Phe Pro	Arg Leu Val Gly	Pro Asp Phe Phe Gly Cys
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Ala Glu Pro Ala Asn Thr	Phe Leu	
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<210> 207

<211> 3074

<212> DNA

<213> Homo sapiens

<400> 207

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<210> 208

<211> 660

<212> PRT

<213> Homo sapiens

<400> 208

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Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu			
35		40	45
Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser			
50		55	60
Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe			
65		70	75
Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr			
85		90	95
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe			
100		105	110
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile			
115		120	125
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe			
130		135	140
Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser			
145		150	155
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp			
165		170	175
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala			
180		185	190
His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp			
195		200	205
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys			
210		215	220
Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn			
225		230	235
Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe			
245		250	255
Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly			
260		265	270
Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly			
275		280	285
Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser			
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Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr			
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325		330	335
Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro			
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Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg			
355		360	365
Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp			
370		375	380
Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val			
385		390	395
Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp			
405		410	415
Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg			
420		425	430
Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser			
435		440	445
Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val			
450		455	460
Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln			
465		470	475
Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr			
485		490	495

Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
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 Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
 515 520 525
 Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
 530 535 540
 Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
 545 550 555 560
 Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
 565 570 575
 Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
 580 585 590
 Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
 595 600 605
 Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
 610 615 620
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 <211> 4160
 <212> DNA
 <213> Homo sapiens

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<210> 210

<211> 328

<212> PRT

<213> Homo sapiens

<400> 210

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Leu Ser Thr Pro Ser Ser Ser Gln Met Gln Ala Arg Lys Lys Arg Arg
35     40     45
Gly Ile Ile Glu Lys Arg Arg Arg Asp Arg Ile Asn Ser Ser Leu Ser
50     55     60
Glu Leu Arg Arg Leu Val Pro Thr Ala Phe Glu Lys Gln Gly Ser Ser
65     70     75     80
Lys Leu Glu Lys Ala Glu Val Leu Gln Met Thr Val Asp His Leu Lys
85     90     95
Met Leu His Ala Thr Gly Gly Thr Gly Phe Phe Asp Ala Arg Ala Leu
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Ala Val Asp Phe Arg Ser Ile Gly Phe Arg Glu Cys Leu Thr Glu Val
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Ile Arg Tyr Leu Gly Val Leu Glu Gly Pro Ser Ser Arg Ala Asp Pro
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165 170 175
Trp Ser Phe Phe His Ser Cys Pro Gly Leu Pro Ala Leu Ser Asn Gln
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Leu Ala Ile Leu Gly Arg Val Pro Ser Pro Val Leu Pro Gly Val Ser
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Ser Pro Ala Tyr Pro Ile Pro Ala Leu Arg Thr Ala Pro Leu Arg Arg
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Ala Thr Gly Ile Ile Leu Pro Ala Arg Arg Asn Val Leu Pro Ser Arg
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Gly Ala Ser Ser Thr Arg Arg Ala Arg Pro Leu Glu Arg Pro Ala Thr
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Pro Val Pro Val Ala Pro Ser Ser Arg Ala Ala Arg Ser Ser His Ile
260 265 270
Ala Pro Leu Leu Gln Ser Ser Ser Pro Thr Pro Pro Gly Pro Thr Gly
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<210> 211

<211> 5680

<212> DNA

<213> Homo sapiens

<400> 211

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<210> 212
 <211> 1331
 <212> PRT
 <213> Homo sapiens

<400> 212

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Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
50      55      60
Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
65      70      75      80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
85      90      95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
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Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
115     120     125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
130     135     140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145     150     155     160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
165     170     175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
180     185     190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
195     200     205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
210     215     220
Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr
225     230     235     240
His His Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
245     250     255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
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Arg Trp Tyr His Asn Arg Ala Pro Val Glu Gly Asp Glu Gln Ala Gly
275     280     285
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Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305     310     315     320
Cys Thr Val Ser Met Ala Gln Gly Asn Ala Ser Lys Lys Val Glu Ile
325     330     335
Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Ala
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<210> 216

<211> 1247

<212> PRT

<213> Homo sapiens

<400> 216

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<212> DNA

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Leu	Gly	Phe	Asp	Gly	Ser	Arg	Asp	Gln	Asn	Val	Phe	Val	Ala	Gln	Lys
				1845				1850				1855			
Gly	Phe	Glu	Ser	Lys	Val	Asp	Ala	Ile	Leu	Asn	Arg	Ile	Ser	Gln	Met
				1860				1865				1870			
His	Arg	Val	Ser	Cys	Ser	Gly	Gly	Arg	Ser	Pro	Thr	Val	Arg	Val	Ser
				1875				1880				1885			
Val	Val	Ala	Asn	Thr	Pro	Ser	Gly	Pro	Val	Glu	Ala	Phe	Asp	Phe	Asp
				1890				1895				1900			
Glu	Tyr	Gln	Pro	Glu	Met	Leu	Glu	Lys	Phe	Arg	Asn	Met	Arg	Ser	Gln
				1905				1910				1915			
His	Pro	Tyr	Val	Leu	Thr	Glu	Asp	Thr	Leu	Lys	Val	Tyr	Leu	Asn	Lys
				1925				1930				1935			
Phe	Arg	Gln	Ser	Ser	Pro	Asp	Ser	Val	Lys	Val	Val	Ile	His	Phe	Thr
				1940				1945				1950			
Asp	Gly	Ala	Asp	Gly	Asp	Leu	Ala	Asp	Leu	His	Arg	Ala	Ser	Glu	Asn
				1955				1960				1965			
Leu	Arg	Gln	Glu	Gly	Val	Arg	Ala	Leu	Ile	Leu	Val	Gly	Leu	Glu	Arg
				1											

Pro Cys Lys Cys Ser Gly Gln Arg Gly Asp Arg Gly Pro Ile Gly Ser
 2035 2040 2045
 Ile Gly Pro Lys Gly Ile Pro Gly Glu Asp Gly Tyr Arg Gly Tyr Pro
 2050 2055 2060
 Gly Asp Glu Gly Gly Pro Gly Glu Arg Gly Pro Pro Gly Val Asn Gly
 2065 2070 2075 2080
 Thr Gln Gly Phe Gln Gly Cys Pro Gly Gln Arg Gly Val Lys Gly Ser
 2085 2090 2095
 Arg Gly Phe Pro Gly Glu Lys Gly Glu Val Gly Glu Ile Gly Leu Asp
 2100 2105 2110
 Gly Leu Asp Gly Glu Asp Gly Asp Lys Gly Leu Pro Gly Ser Ser Gly
 2115 2120 2125
 Glu Lys Gly Asn Pro Gly Arg Arg Gly Asp Lys Gly Pro Arg Gly Glu
 2130 2135 2140
 Lys Gly Glu Arg Gly Asp Val Gly Ile Arg Gly Asp Pro Gly Asn Pro
 2145 2150 2155 2160
 Gly Gln Asp Ser Gln Glu Arg Gly Pro Lys Gly Glu Thr Gly Asp Leu
 2165 2170 2175
 Gly Pro Met Gly Val Pro Gly Arg Asp Gly Val Pro Gly Gly Pro Gly
 2180 2185 2190
 Glu Thr Gly Lys Asn Gly Gly Phe Gly Arg Arg Gly Pro Pro Gly Ala
 2195 2200 2205
 Lys Gly Asn Lys Gly Gly Pro Gly Gln Pro Gly Phe Glu Gly Glu Gln
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 Gly Thr Arg Gly Ala Gln Gly Pro Ala Gly Pro Ala Gly Pro Pro Gly
 2225 2230 2235 2240
 Leu Ile Gly Glu Gln Gly Ile Ser Gly Pro Arg Gly Ser Gly Gly Ala
 2245 2250 2255
 Arg Gly Ala Pro Gly Glu Arg Gly Arg Thr Gly Pro Leu Gly Arg Lys
 2260 2265 2270
 Gly Glu Pro Gly Glu Pro Gly Pro Lys Gly Gly Ile Gly Asn Pro Gly
 2275 2280 2285
 Pro Arg Gly Glu Thr Gly Asp Asp Gly Arg Asp Gly Val Gly Ser Glu
 2290 2295 2300
 Gly Arg Arg Gly Lys Lys Gly Glu Arg Gly Phe Pro Gly Tyr Pro Gly
 2305 2310 2315 2320
 Pro Lys Gly Asn Pro Gly Glu Pro Gly Leu Asn Gly Thr Thr Gly Pro
 2325 2330 2335
 Lys Gly Ile Arg Gly Arg Arg Gly Asn Ser Gly Pro Pro Gly Ile Val
 2340 2345 2350
 Gly Gln Lys Gly Arg Pro Gly Tyr Pro Gly Pro Ala Gly Pro Arg Gly
 2355 2360 2365
 Asn Arg Gly Asp Ser Ile Asp Gln Cys Ala Leu Ile Gln Ser Ile Lys
 2370 2375 2380
 Asp Lys Cys Pro Cys Cys Tyr Gly Pro Leu Glu Cys Pro Val Phe Pro
 2385 2390 2395 2400
 Thr Glu Leu Ala Phe Ala Leu Asp Thr Ser Glu Gly Val Asn Gln Asp
 2405 2410 2415
 Thr Phe Gly Arg Met Arg Asp Val Val Leu Ser Ile Val Asn Val Leu
 2420 2425 2430
 Thr Ile Ala Glu Ser Asn Cys Pro Thr Gly Ala Arg Val Ala Val Val
 2435 2440 2445
 Thr Tyr Asn Asn Glu Val Thr Thr Glu Ile Arg Phe Ala Asp Ser Lys
 2450 2455 2460
 Arg Lys Ser Val Leu Leu Asp Lys Ile Lys Asn Leu Gln Val Ala Leu
 2465 2470 2475 2480
 Thr Ser Lys Gln Gln Ser Leu Glu Thr Ala Met Ser Phe Val Ala Arg
 2485 2490 2495
 Asn Thr Phe Lys Arg Val Arg Asn Gly Phe Leu Met Arg Lys Val Ala
 2500 2505 2510
 Val Phe Phe Ser Asn Thr Pro Thr Arg Ala Ser Pro Gln Leu Arg Glu

2515	2520	2525
Ala Val Leu Lys Leu Ser Asp Ala Gly Ile Thr Pro Leu Phe Leu Thr		
2530	2535	2540
Arg Gln Glu Asp Arg Gln Leu Ile Asn Ala Leu Gln Ile Asn Asn Thr		
2545	2550	2555
Ala Val Gly His Ala Leu Val Leu Pro Ala Gly Arg Asp Leu Thr Asp		2560
2565	2570	2575
Phe Leu Glu Asn Val Leu Thr Cys His Val Cys Leu Asp Ile Cys Asn		
2580	2585	2590
Ile Asp Pro Ser Cys Gly Phe Gly Ser Trp Arg Pro Ser Phe Arg Asp		
2595	2600	2605
Arg Arg Ala Ala Gly Ser Asp Val Asp Ile Asp Met Ala Phe Ile Leu		
2610	2615	2620
Asp Ser Ala Glu Thr Thr Thr Leu Phe Gln Phe Asn Glu Met Lys Lys		2640
2625	2630	2635
Tyr Ile Ala Tyr Leu Val Arg Gln Leu Asp Met Ser Pro Asp Pro Lys		
2645	2650	2655
Ala Ser Gln His Phe Ala Arg Val Ala Val Val Gln His Ala Pro Ser		
2660	2665	2670
Glu Ser Val Ser Met Pro Pro Val Lys Val Glu Phe Ser Leu Thr Asp		
2675	2680	2685
Tyr Gly Ser Lys Glu Lys Leu Val Asp Phe Leu Ser Arg Gly Met Thr		
2690	2695	2700
Gln Leu Gln Gly Thr Arg Ala Leu Gly Ser Ala Ile Glu Tyr Thr Ile		2720
2705	2710	2715
Glu Asn Val Phe Glu Ser Ala Pro Asn Pro Arg Asp Leu Lys Ile Val		
2725	2730	2735
Val Leu Met Leu Thr Gly Glu Val Pro Glu Gln Gln Leu Glu Glu Ala		
2740	2745	2750
Gln Arg Val Ile Leu Gln Ala Lys Cys Lys Gly Tyr Phe Phe Val Val		
2755	2760	2765
Leu Gly Ile Gly Arg Lys Val Asn Ile Lys Glu Val Tyr Thr Phe Ala		
2770	2775	2780
Ser Glu Pro Asn Asp Val Phe Phe Lys Leu Val Asp Lys Ser Thr Glu		2800
2785	2790	2795
Leu Asn Glu Glu Pro Leu Met Arg Phe Gly Arg Leu Leu Pro Ser Phe		
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Val Ser Ser Glu Asn Ala Phe Tyr Leu Ser Pro Asp Ile Arg Lys Gln		
2820	2825	2830
Cys Asp Trp Phe Gln Gly Asp Gln Pro Thr Lys Asn Leu Val Lys Phe		
2835	2840	2845
Gly His Lys Gln Val Asn Val Pro Asn Asn Val Thr Ser Ser Pro Thr		
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Ser Asn Pro Val Thr Thr Thr Lys Pro Val Thr Thr Thr Lys Pro Val		2880
2865	2870	2875
Thr Thr Thr Thr Lys Pro Val Thr Thr Thr Thr Lys Pro Val Thr Ile		
2885	2890	2895
Ile Asn Gln Pro Ser Val Lys Pro Ala Ala Ala Lys Pro Ala Pro Ala		
2900	2905	2910
Lys Pro Val Ala Ala Lys Pro Val Ala Thr Lys Thr Ala Thr Val Arg		
2915	2920	2925
Pro Pro Val Ala Val Lys Pro Ala Thr Ala Ala Lys Pro Val Ala Ala		
2930	2935	2940
Lys Pro Ala Ala Val Arg Pro Pro Ala Ala Ala Lys Pro Val Ala		2960
2945	2950	2955
Thr Lys Pro Glu Val Pro Arg Pro Gln Ala Ala Lys Pro Ala Ala Thr		
2965	2970	2975
Lys Pro Ala Thr Thr Lys Pro Val Val Lys Met Leu Arg Glu Val Gln		
2980	2985	2990
Val Phe Glu Ile Thr Glu Asn Ser Ala Lys Leu His Trp Glu Arg Pro		
2995	3000	3005

Glu Pro Pro Gly Pro Tyr Phe Tyr Asp Leu Thr Val Thr Ser Ala His
 3010 3015 3020
 Asp Gln Ser Leu Val Leu Lys Gln Asn Leu Thr Val Thr Asp Arg Val
 3025 3030 3035 3040
 Ile Gly Gly Leu Leu Ala Gly Gln Thr Tyr His Val Ala Val Val Cys
 3045 3050 3055
 Tyr Leu Arg Ser Gln Val Arg Ala Thr Tyr His Gly Ser Phe Ser Thr
 3060 3065 3070
 Lys Lys Ser Gln Pro Pro Pro Pro Gln Pro Ala Arg Ser Ala Ser Ser
 3075 3080 3085
 Ser Thr Ile Asn Leu Met Val Ser Thr Glu Pro Leu Ala Leu Thr Glu
 3090 3095 3100
 Thr Asp Ile Cys Lys Leu Pro Lys Asp Glu Gly Thr Cys Arg Asp Phe
 3105 3110 3115 3120
 Ile Leu Lys Trp Tyr Tyr Asp Pro Asn Thr Lys Ser Cys Ala Arg Phe
 3125 3130 3135
 Trp Tyr Gly Gly Cys Gly Gly Asn Glu Asn Lys Phe Gly Ser Gln Lys
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 Ser Val Met Gly Thr
 3170

<210> 219

<211> 2806

<212> DNA

<213> Homo sapiens

<400> 219

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gaagcagctt	ctccctcaca	gtctcagaaa	agcgcagggtg	acaaagagag	ggctcttttt	180
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aacacagttt	gctgagccct	ccttcacact	attgaactag	aatccccaac	tgagaaccca	300
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<210> 220

<211> 161

<212> PRT

<213> Homo sapiens

<400> 220

Met	Asn	Leu	Ala	Ile	Ser	Ile	Ala	Leu	Leu	Leu	Thr	Val	Leu	Gln	Val
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Ser	Arg	Gly	Gln	Lys	Val	Thr	Ser	Leu	Thr	Ala	Cys	Leu	Val	Asp	Gln
			20					25					30		
Ser	Leu	Arg	Leu	Asp	Cys	Arg	His	Glu	Asn	Thr	Ser	Ser	Ser	Pro	Ile
		35					40					45			
Gln	Tyr	Glu	Phe	Ser	Leu	Thr	Arg	Glu	Thr	Lys	Lys	His	Val	Leu	Phe
	50					55					60				
Gly	Thr	Val	Gly	Val	Pro	Glu	His	Thr	Tyr	Arg	Ser	Arg	Thr	Asn	Phe
65					70					75					80
Thr	Ser	Lys	Tyr	His	Met	Lys	Val	Leu	Tyr	Leu	Ser	Ala	Phe	Thr	Ser
				85					90					95	
Lys	Asp	Glu	Gly	Thr	Tyr	Thr	Cys	Ala	Leu	His	His	Ser	Gly	His	Ser
			100					105					110		
Pro	Pro	Ile	Ser	Ser	Gln	Asn	Val	Thr	Val	Leu	Arg	Asp	Lys	Leu	Val
		115					120					125			
Lys	Cys	Glu	Gly	Ile	Ser	Leu	Leu	Ala	Gln	Asn	Thr	Ser	Trp	Leu	Leu
	130					135					140				
Leu	Leu	Leu	Leu	Ser	Leu	Ser	Leu	Leu	Gln	Ala	Thr	Asp	Phe	Met	Ser
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Leu															

<210> 221

<211> 736

<212> DNA

<213> Homo sapiens

<400> 221

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agtgggtaca	gcgtgccctt	cacttcgcca	tcagcgagta	caacaaggcc	accgaagatg	240
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ccacccttgg	actgggtggc	cccaccctgc	gggaggcctc	cccatgtgcc	tgtgccaaga	600

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<210> 222
 <211> 594
 <212> DNA
 <213> Homo sapiens

<400> 222
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 ggccctggcc tggagcccca aggaggagga taggataatc ccgggtggca tctataacgc 180
 agacctcaat gatgagtggg tacagcgtgc ccttcacttc gccatcagcg agtataacaa 240
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 cggtgggggg gtgaattact tcttcgacgt agaggtgggc cgaaccatat gtaccaagtc 360
 ccagcccaac ttggacacct gtgccttcca tgaacagcca gaactgcaga agaaacagtt 420
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 gtgtcaagaa tcctagggat ctgtgccagg ccattcgcac cagccaccac ccactccac 540
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<210> 223
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 223
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 Gly Ile Tyr Asp Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
 35 40 45
 His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Glu Asp Glu Tyr Tyr
 50 55 60
 Arg Arg Pro Leu Gln Val Leu Arg Ala Arg Glu Gln Thr Phe Gly Gly
 65 70 75 80
 Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
 85 90 95
 Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
 100 105 110
 Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
 115 120 125
 Asp Arg Met Ser Leu Val Asn Ser Arg Cys Gln Glu Ala
 130 135 140

<210> 224
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 224
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 Gly Ile Tyr Asn Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
 35 40 45
 His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Lys Asp Asp Tyr Tyr
 50 55 60
 Arg Arg Pro Leu Arg Val Leu Arg Ala Arg Gln Gln Thr Val Gly Gly

65	70	75	80
Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys			
	85	90	95
Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu			
	100	105	110
Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu			
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Asn Arg Arg Ser Leu Val Lys Ser Arg Cys Gln Glu Ser			
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<210> 225
 <211> 5460
 <212> DNA
 <213> Homo sapiens

<400> 225

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<211> 1202

<212> PRT

<213> Homo sapiens

<400> 228

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<400> 230

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Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe
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Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val
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Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser Phe Thr Phe Gln Ala Ala
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Ser Asp Ala Phe Met Ile Leu Asn Pro Ser Pro Asp Val Pro Glu Ser
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Lys Val Thr Ser Met Ser Ala Val Glu Phe Thr Pro Leu Pro Thr Cys

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Pro Asp Thr Ser Phe Ser Pro Tyr Asp Gly Asp Leu Thr Thr Thr Ser		365
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Gly His Pro Thr Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro		445
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His His Trp Pro Ala Met Lys Phe Arg Ser His Pro Asp His Ser Thr		460
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 <213> Homo sapiens

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35      40      45
Leu Asp Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr
50      55      60
Phe Val Glu Gln Leu Ala His Lys Phe Ile Ser Pro Gln Leu Arg Met
65      70      75      80
Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
85      90      95
Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
100     105     110
Leu Pro Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser
115     120     125
Glu Gln Ile Tyr Tyr Glu Asn Arg Gln Gly Tyr Arg Thr Ala Ser Val
130     135     140
Ile Ile Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr
145     150     155     160
Ser Glu Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr
165     170     175
Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
180     185     190
Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
195     200     205
Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
210     215     220
Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
225     230     235     240
Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
245     250     255
Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
260     265     270
Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
275     280     285
Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
290     295     300
Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
305     310     315     320
Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
325     330     335
Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
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Glu Val Pro Pro Pro Pro Ala Glu Glu Ser Glu Glu Glu Asp Asp Asp
355     360     365
Gly Leu Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly

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Pro Ile Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly				
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Tyr Asp Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg				
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 65 70 75 80
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 Cys Gln Ser Thr Asn Gly Gln Pro Gln Arg Gly Ala Cys Gly Arg Trp
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 Arg Gly Arg Ser Arg Ser Arg Arg Ala Ala Thr Ser Arg Pro Glu Arg
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 His Thr Arg Pro Asp Arg Asp Arg His Val Ser Ile Val Arg Glu Asn
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<210> 244

<211> 1523

<212> PRT

<213> Homo sapiens

<400> 244

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<211> 4227

<212> DNA

<213> Homo sapiens

<400> 245

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<211> 818

<212> PRT

<213> Homo sapiens

<400> 246

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Glu	Ala	Cys	Val	Thr	Met	Leu	Leu	Glu	Cys	Gly	Met	Gln	Glu	Glu	Gly
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<210> 247
 <211> 2850
 <212> DNA
 <213> Homo sapiens

<400> 247

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 <212> PRT
 <213> Homo sapiens

<400> 248

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Phe	Ile	Glu	Asp	Leu	Lys	Lys	Tyr	Gly	Ala	Thr	Thr	Val	Val	Arg	Val
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Cys	Glu	Val	Thr	Tyr	Asp	Lys	Thr	Pro	Leu	Glu	Lys	Asp	Gly	Ile	Thr
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Val	Leu	Val	Ala	Leu	Ala	Leu	Ile	Glu	Ser	Gly	Met	Lys	Tyr	Glu	Asp
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Ala	Ile	Gln	Phe	Ile	Arg	Gln	Lys	Arg	Arg	Gly	Ala	Ile	Asn	Ser	Lys
		130				135					140				
Gln	Leu	Thr	Tyr	Leu	Glu	Lys	Tyr	Arg	Pro	Lys	Gln	Arg	Leu	Arg	Phe
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<210> 249

<211> 3853

<212> DNA

<213> Homo sapiens

<400> 249

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<210> 250

<211> 1179

<212> PRT

<213> Homo sapiens

<400> 250

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Gly Ser Pro Leu Val Gly Gln Pro Lys Asn Arg Thr Gly Asp Val Tyr
65     70     75     80
Lys Cys Pro Val Gly Arg Gly Glu Ser Leu Pro Cys Val Lys Leu Asp
85     90     95
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Thr Gly Ile Cys Ser Asp Val Ser Pro Thr Phe Gln Val Val Asn Ser

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<212> PRT

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Gly Leu Pro Gly Arg Gly Phe Pro Gly Phe Pro Gly Ala Lys Gly Asp		
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Lys Gly Ser Lys Gly Glu Val Gly Phe Pro Gly Leu Ala Gly Ser Pro		
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Gly Ile Pro Gly Ser Lys Gly Glu Gln Gly Phe Met Gly Pro Pro Gly		
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Pro Gln Gly Gln Pro Gly Leu Pro Gly Ser Pro Gly His Ala Thr Glu		
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Gly Pro Lys Gly Asp Arg Gly Pro Gln Gly Gln Pro Gly Leu Pro Gly		
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Lys Gly Asp Lys Gly Asn Pro Gly Trp Pro Gly Ala Pro Gly Val Pro		
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Gly Asp Gln Gly Asp Gln Gly Val Pro Gly Ala Lys Gly Leu Pro Gly		
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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

<400> 254

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<212> DNA

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<212> PRT

<213> Homo sapiens

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Phe Lys Ile Ile Asp Glu Asn Thr Val His Met Ser Trp Ala Glu Pro
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Val Asp Pro Ile Val Gly Tyr Arg Ile Thr Val Asp Pro Thr Thr Asp
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Phe	Glu	Ser	Leu	Ser	Arg	Ile	Val	Asp	Asp	Leu	Thr	Ile	Asn	Leu	Cys	1365	1370	1375
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Ile	Ser	Glu	Arg	Thr	His	Arg	Ser	Phe	Arg	Val	Ser	Trp	Thr	Pro	Pro	1395	1400	1405
Ser	Asp	Ser	Val	Asp	Arg	Tyr	Lys	Val	Glu	Tyr	Tyr	Pro	Val	Ser	Gly	1410	1415	1420
Gly	Lys	Arg	Gln	Glu	Phe	Tyr	Val	Ser	Arg	Met	Glu	Thr	Ser	Thr	Val	1425	1430	1435
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Thr	Met	His	Val	Gln	Trp	Gln	Pro	Val	Gly	Gly	Ala	Thr	Gly	Tyr	Ile	1490	1495	1500
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165

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 Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
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 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
 260 265 270
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 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
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<210> 261

<211> 1464

<212> PRT

<213> Homo sapiens

<400> 261

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Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His
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Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp
 50          55          60
Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn
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Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro
 85          90          95
Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly
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 1345 1350 1355 1360
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<211> 2574

<212> DNA

<213> Homo sapiens

<400> 262

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<210> 263

<211> 412

<212> PRT

<213> Homo sapiens

<400> 263

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Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
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Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn Thr
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Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
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Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr
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Ile	His	Cys	Pro	Cys	His	Thr	Phe	Gln	Pro	Asn	Gly	Asp	Ile	Leu	Glu
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Asp	Asp	His	Gly	Arg	Gly	Asp	Leu	Gly	Arg	Leu	Lys	Lys	Gln	Lys	Asp
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<211> 5086
<212> DNA
<213> Homo sapiens
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<400> 264

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<210> 265
 <211> 1366
 <212> PRT
 <213> Homo sapiens

<400> 265

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Pro	Gln	Gly	Ala	Arg	Gly	Phe	Pro	Gly	Thr	Pro	Gly	Leu	Pro	Gly	Phe
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 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
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 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
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 Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
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Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala				
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	1300		1305	
Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile				
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Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile				
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 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 50 55 60
 Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu Ser

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Thr	Gly	Ser	Lys	Ala	Gln	Asp	Thr	Ala	Arg	Gly	Lys	Gly	Lys	Asp
			245						250					255
Ser	Lys	Tyr	Gly	Ser	Val	Gln	Lys	Ser	Phe	Ala	Asp	Arg	Gly	Leu
			260					265					270	
Lys	Pro	Pro	Lys	Glu	Lys	Leu	Leu	Gln	Val	Glu	Lys	Leu	Arg	Lys
	275						280					285		
Ser	Gly	Lys	Gly	Ser	Phe	Leu	Gln	Pro	Thr	Ala	Lys	Pro	Arg	Ala
	290					295					300			
Ala	Gln	Gln	Gln	Ala	Val	Ile	Arg	Gly	Phe	Thr	Tyr	Tyr	Lys	Ala
305					310					315				Gly
Lys	Gln	Glu	Val	Thr	Glu	Ala	Val	Ala	Asp	Asn	Thr	Leu	Gln	Gly
				325					330					335
Ser	Trp	Leu	Glu	Gln	Leu	Pro	Pro	Lys	Val	Glu	Gly	Arg	Ser	Asn
			340					345					350	
Ala	Glu	Pro	Asn	Ser	Ala	Glu	Gln	Asp	Glu	Ala	Glu	Pro	Arg	Ser
	355						360					365		
Glu	Arg	Val	Asp	Leu	Ala	Ser	Gly	Thr	Pro	Thr	Ser	Ile	Pro	Ala
	370					375						380		
Thr	Thr	Thr	Ala	Thr	Thr	Thr	Pro	Thr	Pro	Thr	Thr	Ser	Leu	Leu
385					390					395				400
Thr	Glu	Pro	Pro	Ser	Gly	Pro	Glu	Val	Ser	Ser	Gln	Gly	Arg	Glu
				405					410					415
Ser	Cys	Glu	Gly	Thr	Leu	Arg	Ala	Val	Asp	Pro	Pro	Val	Arg	His
			420					425					430	His
Ser	Tyr	Gly	Arg	His	Glu	Gly	Ala	Trp	Met	Lys	Asp	Pro	Ala	Ala
	435						440					445		Arg
Asp	Asp	Arg	Ile	Tyr	Val	Thr	Asn	Tyr	Tyr	Tyr	Gly	Asn	Ser	Leu
	450					455					460			Val
Glu	Phe	Arg	Asn	Leu	Glu	Asn	Phe	Lys	Gln	Gly	Arg	Trp	Ser	Asn
465					470					475				Met
Tyr	Lys	Leu	Pro	Tyr	Asn	Trp	Ile	Gly	Thr	Gly	His	Val	Val	Tyr
				485					490					Gln
Gly	Ala	Phe	Tyr	Tyr	Asn	Arg	Ala	Phe	Thr	Lys	Asn	Ile	Ile	Lys
			500					505				510		Tyr
Asp	Leu	Arg	Gln	Arg	Phe	Val	Ala	Ser	Trp	Ala	Leu	Leu	Pro	Asp
	515						520					525		Val
Val	Tyr	Glu	Asp	Thr	Thr	Pro	Trp	Lys	Trp	Arg	Gly	His	Ser	Asp
	530					535					540			Ile
Asp	Phe	Ala	Val	Asp	Glu	Ser	Gly	Leu	Trp	Val	Ile	Tyr	Pro	Ala
545					550					555				Val
														560

Asp Asp Arg Asp Glu Ala Gln Pro Glu Val Ile Val Leu Ser Arg Leu
 565 570 575
 Asp Pro Gly Asp Leu Ser Val His Arg Glu Thr Thr Trp Lys Thr Arg
 580 585 590
 Leu Arg Arg Asn Ser Tyr Gly Asn Cys Phe Leu Val Cys Gly Ile Leu
 595 600 605
 Tyr Ala Val Asp Thr Tyr Asn Gln Gln Glu Gly Gln Val Ala Tyr Ala
 610 615 620
 Phe Asp Thr His Thr Gly Thr Asp Ala Arg Pro Gln Leu Pro Phe Leu
 625 630 635 640
 Asn Glu His Ala Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg
 645 650 655
 Val Leu Tyr Ala Trp Asp Asn Gly His Gln Leu Thr Tyr Thr Leu His
 660 665 670
 Phe Val Val
 675

<210> 268
 <211> 1909
 <212> DNA
 <213> Homo sapiens

<400> 268
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 tctactgtat gaattatgct ttaagtagaa ttcagtgcca aggagaactt ggtgaaataa 180
 attattttta tttttttttt atcctttaca aagccatgga ttttatttgg ttgatgtgtg 240
 ctctgtacac aagccatttc aataggatgg agctgttaat tattttccaa agagtaatag 300
 acatgcaaaa gtttcaataa aaactgggcc attaacaat aaattaataa actaataagc 360
 attcccttct aggtttttgc caaactgcct atccaataac aaatttgaga atcgttgaaa 420
 aagctagtta tttttcagag aaatgatttt cattattgaa actgttctcc ctagcaggcc 480
 attttccctt tttcctggga gtttagcaag tttaggagag aatagtcattg aaaagaaagg 540
 gaagaaaggg gagaagggaa gaggttaaaa agtaagtgtc cagacctatg aacgtaatcc 600
 ctttgctaga aatattttaag agcagctcag cttgggtgaa actgagtttt gtcattcttc 660
 atatttgcag gaaggtattt tctgacttgc aatgcagcta gatgtaaaat tttattttat 720
 catcctagaa agccttgact agaaaaatga ataaatattg aggggttctt gtccatatct 780
 ggcttgcatg tgccagaaag cagagaatag aaaatgtaat ctccaacatc caagcatcga 840
 aacccaaggg gtaggcaatt ctatgtagg tttggacatg aagtttggtg catcttggtt 900
 tatgtctggc caactgctat taaacctctc tggcttatag tctcttcatt ctattagaca 960
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 caacaacaac gacaacaaca aacatttgga atattattct caactcacgt tttataataa 1260
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 gtttaataag cctcttgcaa gttacttggt ctctcacctg aggtattttt ttcctcccca 1380
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 ggggtccaact tcaataatgt aataattaat acattaaaag catttaactt cctttctaga 1500
 aaaatgcaca ggctaaggca tagacaaaac aaagagaaat gctgagaaat ttgccactgg 1560
 agacaagcaa tctgaataaa tttttgccaa aagttctttt tatgtcatat agtgtcagga 1620
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 aggagaatga agtagaagtg aaaggtttat aaatccattt gtaagcattt atcccatata 1740
 ttttaaatc aagaaaaatt gtgtttatct ttagaatttt gtattcaata ctttatgtac 1800
 tatgtgactc atgcttctgg ataaataaag caccaaatat gtatctgtaa ccacaatcac 1860
 acatattata ttaaataatat atctatataa caaaaaaaaaa aaaaaaaaaa 1909

<210> 269
 <211> 83
 <212> PRT
 <213> Homo sapiens

<400> 269

Met Tyr Gly Asn Ile Leu Cys Pro Thr Leu His Thr Leu Cys Thr Gln
 1 5 10 15
 Ile Leu Tyr Cys Met Asn Tyr Ala Leu Ser Arg Ile Gln Cys Gln Gly
 20 25 30
 Glu Leu Gly Glu Ile Asn Tyr Phe Asn Phe Phe Phe Ile Leu Tyr Lys
 35 40 45
 Ala Met Asp Phe Ile Trp Leu Met Cys Ala Leu Tyr Thr Ser His Phe
 50 55 60
 Asn Arg Met Glu Leu Leu Ile Ile Phe Gln Arg Val Ile Asp Met Gln
 65 70 75 80
 Lys Phe Gln

<210> 270

<211> 1720

<212> DNA

<213> Homo sapiens

<400> 270

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 tgggtgaatat ctctgaacct gggcatgaaa cagagagatg tcctaactct gggtagagagg 180
 aatcctcatt tttctctgcc ctctcactgt ggcacccctaa gaaaaaagtt ttgggttcct 240
 gcagcatgaa ggagagctct gctcccagaa tttgggagct ccagatttct tccaggggtgt 300
 ggagggcatca atatatcagt ctgggaaagg ggttcctggg ccactccagg agctgagttg 360
 ggtggaagggt gctgagagtg tgggtggggg ccacttctga gcacccatgt ggcacccact 420
 gctggtccct gtttgtggct gggcactcag gaaaatgttt ttggtgctaa gagtaaaaag 480
 ccaaccaaca aacacatctc ttttttctgt ctattcactg gaaagtaaaa gcagtctggg 540
 cgcaggctgg ggaccagat ggaattcaaa cttatgcctg ctctcaagggt gctcacgggt 600
 gctgataaac agctggataa aatgaagagt ctatgagtga gggatgcaga gccagggaag 660
 gctggtggag tgatgccacc agcacagggg tatgagtttg cagctgccaa ggggccaaagg 720
 gatgagctgg ggccctcctt cccaatggca tctccccctg gtctggaact gaagacactg 780
 agcaatggtc cccaagcccc aaggagatca gctccccctg gccagtggtc cccaaccagg 840
 gagggtgtgg agaatgcctg cttctcctca gaggagcatg agaccattt ccagaaccct 900
 gggaacacga gactgggcag ctcaccaggt cccctgggg gtgtctcctc actgccccga 960
 tcccagcggg atgatctgtc ctttcattca gaggaggggc cagccctgga gcccgtagc 1020
 cgccccgtgg attatggctt tgtttcggc ctggttttcc tggtagtggt gattcttctg 1080
 ctggttgacag catacgccat ccccggtgac atccggacac agtgacagcg 1140
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 gtctccctgt gcaagggcga gctgtaccgc cggaggacct tcgtccccgg caagggctcc 1320
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 gccctggtgg agaatgaagt tgtccaggtc tcagagacta gccacaccct ccagaggtct 1440
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 atggcttctg ctgctaaaaa tacaaaagtt tggaaaccgc 1720

<210> 271

<211> 256

<212> PRT

<213> Homo sapiens

<400> 271

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 Asp Glu Leu Gly Pro Ser Phe Pro Met Ala Ser Pro Pro Gly Leu Glu
 20 25 30
 Leu Lys Thr Leu Ser Asn Gly Pro Gln Ala Pro Arg Arg Ser Ala Pro

1	5	10	15
Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala			
20		25	30
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys			
35		40	45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu			
50		55	60
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp			
65	70	75	80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu			
85		90	95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys			
100		105	110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys			
115		120	125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln			
130		135	140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg			
145	150	155	160
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu			
165		170	175
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu			
180		185	190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu			
195		200	205
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu			
210		215	220
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu			
225	230	235	240
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu			
245		250	255
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu			
260		265	270
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile			
275		280	

<210> 274

<211> 2032

<212> DNA

<213> Homo sapiens

<400> 274

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gcgacccagc	aggacaagca	ggacattgac	aagcagtagc	tgggcttcgc	cacactgccc	180
aaccaggtgc	accgcaagtc	ggtgaagaaa	ggctttgact	tcacactcat	ggtggctggt	240
gagtcaggcc	tggggaagtc	cacactggtc	cacagcctct	tcctgacaga	cttgtagaag	300
gaccggaagc	tgctcagtc	tgaggagcgc	atcagccaga	cggtagagat	tctaaaacac	360
acgggtggaca	ttgaggagaa	gggagtcagg	ctgaagctca	ccatcgtaga	cacgcccggg	420
ttcggggagc	ctgtcaacaa	caccgagtcg	tggaagccca	tcaccgacta	tgtggaccag	480
cagtttgagc	agtacttccg	tgatgagagc	ggcctcaacc	gaaagaacat	ccaagacaac	540
cgagtgacac	gtgcctata	cttcattccc	cccttcgggc	atgggctgcg	gccagtggtg	600
tggtggtttca	tgaaggcatt	gcattgagag	gtcaacatcg	tgctctctcat	cgccaaagct	660
gactgtcttg	tccccagtg	gatccggaag	ctgaaggagc	ggatccggga	ggagattgac	720
aagtttgagg	tccatgtata	ccagttccct	gagtgtagct	cggacgagga	tgaggacttc	780
aagcagcagg	accgggaact	gaaggagagc	gcgcccttcg	ccgttatagg	cagcaacacg	840
gtgggtggagg	ccaaggggca	gcgggtccgg	ggccgactgt	acccctgggg	gatcgtggag	900
gtggagaacc	aggcgcatcg	cgacttcgtg	aagctgcgca	acatgctcat	ccgcacgcac	960
atgcacgacc	tcaaggacgt	gacgtgcgac	gtgcactacg	agaactaccg	cgcgactgac	1020
atccagcaga	tgaccagcaa	actgaccagc	gacagccgca	tgagagagcc	catcccgatc	1080
ctgccgctgc	ccaccccgga	cgccgagact	gagaagctta	tcaggatgaa	ggatgaggaa	1140

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ctgaggcgca tgcaggagat gctgcagagg atgaagcagc agatgcagga ccagtgcgc 1200
tcgcccgga cacaccgtcc gtctccggga cgccctcgca cccctggaca ccagaccgga 1260
ctgttccga cccggagacg cggggccaca gcccagct gaccctaatt tattctcagc 1320
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agctggccct ctctgacctt gggggatcag gagcgaagtt gggcgggact tcagagatcc 1440
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gagtgtgag accccatttt ctgtcgaggc gggccgagtc ttcccttatc cccagacgcc 1680
tagcgggagc ggttgggctg aatcaaagtg gagccctcca gacataagga ggccagaggc 1740
tgcaaggagc ggggtcgtga ccgcttacac cccttctcca cagcccgcc cgacctggag 1800
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ctcccgatgt tcccaccgc atgatccctt cccgccacac gatgtccgt tttcttccgt 1980
tgtgaatgcc gcgtcctgtc ctggtgacag gagaacaatg ttggtgaacg tc 2032

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<210> 275

<211> 369

<212> PRT

<213> Homo sapiens

<400> 275

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20
Gln Val His Arg Lys Ser Val Lys Lys Gly Phe Asp Phe Thr Leu Met
35      40      45
Val Ala Gly Glu Ser Gly Leu Gly Lys Ser Thr Leu Val His Ser Leu
50      55      60
Phe Leu Thr Asp Leu Tyr Lys Asp Arg Lys Leu Leu Ser Ala Glu Glu
65      70      75      80
Arg Ile Ser Gln Thr Val Glu Ile Leu Lys His Thr Val Asp Ile Glu
85      90      95
Glu Lys Gly Val Lys Leu Lys Leu Thr Ile Val Asp Thr Pro Gly Phe
100      105      110
Gly Asp Ala Val Asn Asn Thr Glu Cys Trp Lys Pro Ile Thr Asp Tyr
115      120      125
Val Asp Gln Gln Phe Glu Gln Tyr Phe Arg Asp Glu Ser Gly Leu Asn
130      135      140
Arg Lys Asn Ile Gln Asp Asn Arg Val His Cys Cys Leu Tyr Phe Ile
145      150      155      160
Ser Pro Phe Gly His Gly Leu Arg Pro Val Asp Val Gly Phe Met Lys
165      170      175
Ala Leu His Glu Lys Val Asn Ile Val Pro Leu Ile Ala Lys Ala Asp
180      185      190
Cys Leu Val Pro Ser Glu Ile Arg Lys Leu Lys Glu Arg Ile Arg Glu
195      200      205
Glu Ile Asp Lys Phe Gly Ile His Val Tyr Gln Phe Pro Glu Cys Asp
210      215      220
Ser Asp Glu Asp Glu Asp Phe Lys Gln Gln Asp Arg Glu Leu Lys Glu
225      230      235      240
Ser Ala Pro Phe Ala Val Ile Gly Ser Asn Thr Val Val Glu Ala Lys
245      250      255
Gly Gln Arg Val Arg Gly Arg Leu Tyr Pro Trp Gly Ile Val Glu Val
260      265      270
Glu Asn Gln Ala His Cys Asp Phe Val Lys Leu Arg Asn Met Leu Ile
275      280      285
Arg Thr His Met His Asp Leu Lys Asp Val Thr Cys Asp Val His Tyr
290      295      300
Glu Asn Tyr Arg Ala His Cys Ile Gln Gln Met Thr Ser Lys Leu Thr

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305		310		315		320
Gln Asp Ser Arg Met Glu Ser Pro Ile Pro Ile Leu Pro Leu Pro Thr						
	325			330		335
Pro Asp Ala Glu Thr Glu Lys Leu Ile Arg Met Lys Asp Glu Glu Leu						
	340		345			350
Arg Arg Met Gln Glu Met Leu Gln Arg Met Lys Gln Gln Met Gln Asp						
	355		360			365
Gln						

<210> 276
 <211> 1344
 <212> DNA
 <213> Homo sapiens

<400> 276

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ctggaaaggg	aaaaaaggca	gcattcacca	catcccaatc	ctgaatccaa	gagtctaaga	120
tagtccccca	ctcctatctc	aggcttagag	gattagatta	atctcctgga	gggaagactc	180
ttccttgaaa	catttttttt	tatctgcctg	tagctattgg	gataattcgg	gaaatccaca	240
gggacagttc	aagtcattct	tgtcctctac	tttctgttgc	actctcagcc	ttgttctctt	300
tttagaaact	gcatggtaac	tattatatag	ctaaagaaga	gcattctgac	ctctgccctg	360
ggacttcctg	gatcctcctc	ttcttataaa	tacaagggca	gagctggtat	cccggggagc	420
caggaagcag	tgagcccagg	agtcctcggc	cagccctgcc	tgcccaccag	gaggatgaag	480
gtctccgtgg	ctgccctctc	ctgcctcatg	cttggtgctg	tccttggatc	ccaggcccag	540
ttcacaaatg	atgcagagac	agagttaatg	atgtcaaagc	ttccactgga	aaatccagta	600
gttctgaaca	gctttcactt	tgctgctgac	tgctgcacct	cctacatctc	acaaagcatc	660
ccgtgttcac	tcatgaaaag	ttattttgaa	acgagcagcg	agtgtcccaa	gccagggtgc	720
atattcctca	ccaagaaggg	gcggcaagtc	tgtgccaaac	ccagtgggtc	gggagttcag	780
gattgcatga	aaaagctgaa	gccctactca	atataataat	aaagagacaa	aagaggccag	840
ccaccacact	ccaacacctc	ctgagcctct	gaagctccca	ccaggccagc	tctcctccca	900
caacagcttc	ccacagcatg	aagatctccg	tggttgccat	tcccttcttc	ctcctcatca	960
ccatcgccct	agggaccaa	actgaatcct	cctcacgggg	accttaccac	ccctcagat	1020
gctgcttcac	ctacactacc	tacaagatcc	cgcgtcagcg	gattatggat	tactatgaga	1080
ccaacagcca	gtgctccaag	cccgaattg	tcttcacac	caaaaggggc	cattccgtct	1140
gtaccaaccc	cagtgacaag	tgggtccagg	actatatcaa	ggacatgaag	gagaactgag	1200
tgaccagaaa	gggggtggcg	aggcacagct	cagagacata	aagagaagat	gccaaaggcc	1260
cctcctccac	ccaccgctaa	ctctcagccc	cagtcaccct	cttgagactt	ccctgctttg	1320
aattaaagac	cactcatgct	cttc				1344

<210> 277
 <211> 93
 <212> PRT
 <213> Homo sapiens

<400> 277

Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile											
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Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro											
	20				25				30		
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg											
	35				40				45		
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile											
	50			55				60			
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp											
	65		70			75			80		
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn											
		85				90					

<210> 278
 <211> 1344

<212> DNA

<213> Homo sapiens

<400> 278

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tagtccccca	ctcctatctc	aggcttagag	gattagatta	atctcctgga	gggaagactc	180
ttccttgaaa	catttttttt	tatctgcctg	tagctattgg	gataattcgg	gaaatccaca	240
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tttagaaact	gcatggtaac	tattatatag	ctaaagaaga	gcattctgac	ctctgccctg	360
ggacttcctg	gacctcctc	ttcttataaa	tacaagggca	gagctggtat	cccggggagc	420
caggaagcag	tgagcccagg	agtcctcggc	cagccctgcc	tgcccaccag	gaggatgaag	480
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gttctgaaca	gctttcactt	tgctgctgac	tgctgcacct	cctacatctc	acaaagcatc	660
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ccacccacct	ccaacacctc	ctgagcctct	gaagctccca	ccaggccagc	tctcctccca	900
caacagcttc	ccacagcatg	aagatctccg	tggctgccat	tccttctctc	ctcctcatca	960
ccatcccgct	agggaccaag	actgaatcct	cctcacgggg	accttaccac	ccctcagagt	1020
gctgcttcac	ctacactacc	tacaagatcc	cgcgtcagcg	gattatggat	tactatgaga	1080
ccaacagcca	gtgctccaag	cccggaattg	tcttcatcac	caaaaggggc	cattccgtct	1140
gtaccaaccc	cagtgacaag	tgggtccagg	actatatcaa	ggacatgaag	gagaactgag	1200
tgaccagaaa	ggggtggcga	aggcacagct	cagagacata	aagagaagat	gccaaaggcc	1260
cctcctccac	ccaccgctaa	ctctcagccc	cagtcaccct	cttgagactt	ccctgctttg	1320
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<210> 279

<211> 93

<212> PRT

<213> Homo sapiens

<400> 279

Met	Lys	Ile	Ser	Val	Ala	Ala	Ile	Pro	Phe	Phe	Leu	Leu	Ile	Thr	Ile
1				5					10					15	
Ala	Leu	Gly	Thr	Lys	Thr	Glu	Ser	Ser	Ser	Arg	Gly	Pro	Tyr	His	Pro
			20					25					30		
Ser	Glu	Cys	Cys	Phe	Thr	Tyr	Thr	Thr	Tyr	Lys	Ile	Pro	Arg	Gln	Arg
		35					40					45			
Ile	Met	Asp	Tyr	Tyr	Glu	Thr	Asn	Ser	Gln	Cys	Ser	Lys	Pro	Gly	Ile
	50					55					60				
Val	Phe	Ile	Thr	Lys	Arg	Gly	His	Ser	Val	Cys	Thr	Asn	Pro	Ser	Asp
65					70					75				80	
Lys	Trp	Val	Gln	Asp	Tyr	Ile	Lys	Asp	Met	Lys	Glu	Asn			
				85					90						

<210> 280

<211> 1344

<212> DNA

<213> Homo sapiens

<400> 280

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tagtccccca	ctcctatctc	aggcttagag	gattagatta	atctcctgga	gggaagactc	180
ttccttgaaa	catttttttt	tatctgcctg	tagctattgg	gataattcgg	gaaatccaca	240
gggacagttc	aagtcattctt	tgctcctctac	tttctgttgc	actctcagcc	ttgttctctt	300
tttagaaact	gcatggtaac	tattatatag	ctaaagaaga	gcattctgac	ctctgccctg	360
ggacttcctg	gacctcctc	ttcttataaa	tacaagggca	gagctggtat	cccggggagc	420
caggaagcag	tgagcccagg	agtcctcggc	cagccctgcc	tgcccaccag	gaggatgaag	480

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gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc 660
ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccagggtgc 720
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gattgcatga aaaagctgaa gccctactca atataataat aaagagacaa aagaggccag 840
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caacagcttc ccacagcatg aagatctccg tggctgccat tcccttcttc ctctcatca 960
ccatcgccct agggaccaag actgaatcct cctcacgggg accttaccac ccctcagagt 1020
gctgcttcac ctacactacc tacaagatcc cgcgtcagcg gattatggat tactatgaga 1080
ccaacagcca gtgctccaag cccggaattg tcttcacac caaaaggggc cattccgtct 1140
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tgaccagaa ggggtggcga aggcacagct cagagacata aagagaagat gccaaaggcc 1260
cctcctccac ccaccgctaa ctctcagccc cagtcaccct cttggagctt ccctgctttg 1320
aattaaagac cactcatgct cttc 1344

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<210> 281

<211> 93

<212> PRT

<213> Homo sapiens

<400> 281

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Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1      5      10      15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20     25     30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35     40     45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50     55     60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65     70     75     80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85     90

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<210> 282

<211> 2750

<212> DNA

<213> Homo sapiens

<400> 282

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gagagaaaac agttaataaa aaactaattt aatacaaat ttagctgggc ttggtggcac 180
atgcctgtaa tcccagctac tcgggagggt gaagcaggag agttgcttga acctgggagg 240
cgtagattgc agtgagccaa gatcatcca ctgcactcca gcctgggcca cagagtgaga 300
cacagtctca aacaaaacaa aacaaaaagg aatttagagt agcccatggg gtagctatgc 360
ttaccaacat ccagtgggat ccccgtagat tctccctacc cctttttaag aggattgttg 420
ctaccttcta gggctccgtt tacagggatc actgatttct cagtcacgaa gaacaaaatt 480
atccagcttt gcttggacct gaccactaca gtccagaagg attgctttgt agcggaatg 540
gaggataaag ttttaactgt ggtcaagggt ttaaattggc tctgtgacaa aacaatccga 600
tctaccacag atcctgtgat gagccagtgt gcatgtctgg aggaagtcca cttaccaaac 660
attaaacctg cgggaaggcct gggcatgtac atcaaatcaa cctatgatgg gttcacctg 720
attactggaa ccacagaaaa ttctcctgca gacagatctc agaagattca tgctggtgac 780
gaagtcattc aagttaatca gcaaaactgt gtgggatggc agctgaaaaa tctggtgaag 840
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gagaagttag ccatcctgga tctttatatt cctcctccgc ctgctgttcc ctactctccc 1080
cgggatgaga atggcagttt tgtttatgga gggtccagta agtgcaaaaca accattgcct 1140
ggtcctaagg gttcagagtc cccgaattcc ttcttgacc aggaaagccg gagacgaaga 1200

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gatgggaact ggatggggat tgtggaccct tttgccagac ctcgagggtca tggcaggaaa 1380
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<210> 283

<211> 380

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(380)

<223> Xaa = Any Amino Acid

<400> 283

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Asp Lys Thr Ile Arg Ser Thr Thr Asp Pro Val Met Ser Gln Cys Ala
20     25     30
Cys Leu Glu Glu Val His Leu Pro Asn Ile Lys Pro Gly Glu Gly Leu
35     40     45
Gly Met Tyr Ile Lys Ser Thr Tyr Asp Gly Leu His Val Ile Thr Gly
50     55     60
Thr Thr Glu Asn Ser Pro Ala Asp Arg Ser Gln Lys Ile His Ala Gly
65     70     75     80
Asp Glu Val Ile Gln Val Asn Gln Gln Thr Val Val Gly Trp Gln Leu
85     90     95
Lys Asn Leu Val Lys Lys Leu Arg Glu Asn Pro Thr Gly Val Val Leu
100    105    110
Leu Leu Lys Lys Arg Pro Thr Gly Ser Phe Asn Phe Thr Pro Ala Pro
115    120    125
Leu Lys Asn Leu Arg Trp Lys Pro Pro Leu Val Gln Thr Ser Pro Pro
130    135    140
Pro Ala Thr Thr Gln Ser Pro Glu Ser Thr Met Asp Thr Ser Leu Lys
145    150    155    160
Lys Glu Lys Ser Ala Ile Leu Asp Leu Tyr Ile Pro Pro Pro Pro Ala
165    170    175
Val Pro Tyr Ser Pro Arg Asp Glu Asn Gly Ser Phe Val Tyr Gly Gly

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<400> 284						
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tgctctagtt	tctctctcag	gataaagagt	gaatagaggc	cgaagggtga	atttcttatt	1680
atacataaaa	cactctgtata	tattttgtata	aaggaagcta	agaattttat	tttattttgca	1740

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<210> 285
 <211> 335
 <212> PRT
 <213> Homo sapiens

<400> 285
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 1 5 10 15
 Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
 20 25 30
 Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140
 Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
 145 150 155 160
 Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
 165 170 175
 Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
 180 185 190
 Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
 195 200 205
 Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
 210 215 220
 Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
 225 230 235 240
 Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
 245 250 255
 Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
 260 265 270
 Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
 275 280 285
 Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro Cys Thr
 290 295 300
 Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val Gln Glu
 305 310 315 320
 Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu Ser
 325 330 335

<210> 286
 <211> 305
 <212> PRT
 <213> Homo sapiens

<400> 286
 Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
 1 5 10 15
 Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
 20 25 30

Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140
 Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
 145 150 155 160
 Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
 165 170 175
 Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
 180 185 190
 Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
 195 200 205
 Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
 210 215 220
 Trp Pro Gly Cys Arg Thr Asp Pro Ser Gly Lys Thr Asn His Tyr Gln
 225 230 235 240
 Thr Thr Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys
 245 250 255
 Pro Gly Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro
 260 265 270
 Cys Thr Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val
 275 280 285
 Gln Glu Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu
 290 295 300
 Ser
 305

<210> 287
 <211> 298
 <212> PRT
 <213> Homo sapiens

<400> 287
 Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
 1 5 10 15
 Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
 20 25 30
 Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
 35 40 45
 Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
 50 55 60
 Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
 65 70 75 80
 Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
 85 90 95
 Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
 100 105 110
 Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
 115 120 125
 Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
 130 135 140

Glu	Ile	Lys	Val	Leu	Asn	Lys	Thr	Gln	Glu	Asn	Gly	Thr	Cys	Thr	Leu
145					150					155					160
Ile	Leu	Gly	Cys	Thr	Val	Glu	Lys	Gly	Asp	His	Val	Ala	Tyr	Ser	Trp
				165					170						175
Ser	Glu	Lys	Ala	Gly	Thr	His	Pro	Leu	Asn	Pro	Ala	Asn	Ser	Ser	His
			180					185					190		
Leu	Leu	Ser	Leu	Thr	Leu	Gly	Pro	Gln	His	Ala	Asp	Asn	Ile	Tyr	Ile
		195					200					205			
Cys	Thr	Val	Ser	Asn	Pro	Ile	Ser	Asn	Asn	Ser	Gln	Thr	Phe	Ser	Pro
	210					215					220				
Trp	Pro	Gly	Cys	Arg	Thr	Asp	Pro	Ser	Glu	Thr	Lys	Pro	Trp	Ala	Val
225					230					235					240
Tyr	Ala	Gly	Leu	Leu	Gly	Gly	Val	Ile	Met	Ile	Leu	Ile	Met	Val	Val
			245						250					255	
Ile	Leu	Gln	Leu	Arg	Arg	Arg	Gly	Lys	Thr	Asn	His	Tyr	Gln	Thr	Thr
			260					265					270		
Val	Glu	Lys	Lys	Ser	Leu	Thr	Ile	Tyr	Ala	Gln	Val	Gln	Lys	Pro	Gly
		275					280					285			
Asp	Thr	His	His	Gln	Thr	Ser	Asp	Leu	Phe						
	290					295									

<210> 288

<211> 3640

<212> DNA

<213> Homo sapiens

<400> 288

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<211> 628

<212> PRT

<213> Homo sapiens

<400> 289

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Ala	Cys	Asn	Pro	Arg	Met	Gly	Asn	Leu	Ala	Leu	Gly	Arg	Lys	Leu	Trp
			35				40						45		
Ala	Asp	Thr	Thr	Cys	Gly	Gln	Asn	Ala	Thr	Glu	Leu	Tyr	Cys	Phe	Tyr
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Ser	Glu	Asn	Thr	Asp	Leu	Thr	Cys	Arg	Gln	Pro	Lys	Cys	Asp	Lys	Cys
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Asn	Ala	Ala	Tyr	Pro	His	Leu	Ala	His	Leu	Pro	Ser	Ala	Met	Ala	Asp
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Ser	Ser	Phe	Arg	Phe	Pro	Arg	Thr	Trp	Trp	Gln	Ser	Ala	Glu	Asp	Val
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His	Leu	Ile	Val	Met	Phe	Lys	Ser	Pro	Arg	Pro	Ala	Ala	Met	Val	Leu
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Ala	Thr	Asn	Cys	Ser	Ala	Thr	Phe	Gly	Leu	Glu	Asp	Asp	Val	Val	Lys
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Pro Val His Gly Phe Arg Pro Val Lys Ala Pro Gly Thr Phe His Met	275	280
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Val His Gly Lys Cys Met Cys Lys His Asn Thr Ala Gly Ser His Cys	290	295
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Gln His Cys Ala Pro Leu Tyr Asn Asp Arg Pro Trp Glu Ala Ala Asp	305	310
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Gly Lys Thr Gly Ala Pro Asn Glu Cys Arg Thr Cys Lys Cys Asn Gly	320	325
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His Ala Asp Thr Cys His Phe Asp Val Asn Val Trp Glu Ala Ser Gly	335	340
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Asn Arg Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Glu Gly	350	355
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Gln Tyr Cys Gln Arg Cys Lys Pro Gly Phe Tyr Arg Asp Leu Arg Arg	365	370
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Pro Phe Ser Ala Pro Asp Ala Cys Lys Pro Cys Ser Cys His Pro Val	380	385
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Gly Ser Ala Val Leu Pro Ala Asn Ser Val Thr Phe Cys Asp Pro Ser	395	400
395	400	405
Asn Gly Asp Cys Pro Cys Lys Pro Gly Val Ala Gly Arg Arg Cys Asp	410	415
410	415	420
Arg Cys Met Val Gly Tyr Trp Gly Phe Gly Asp Tyr Gly Cys Arg Pro	425	430
425	430	435
Cys Asp Cys Ala Gly Ser Cys Asp Pro Ile Thr Gly Asp Cys Ile Ser	440	445
440	445	450
Ser His Thr Asp Ile Asp Trp Tyr His Glu Val Pro Asp Phe Arg Pro	455	460
455	460	465
Val His Asn Lys Ser Glu Pro Ala Trp Glu Trp Glu Asp Ala Gln Gly	470	475
470	475	480
Phe Ser Ala Leu Leu His Ser Gly Lys Cys Glu Cys Lys Glu Gln Thr	485	490
485	490	495
Leu Gly Asn Ala Lys Ala Phe Cys Gly Met Lys Tyr Ser Tyr Val Leu	500	505
500	505	510
Lys Ile Lys Ile Leu Ser Ala His Asp Lys Gly Thr His Val Glu Val	515	520
515	520	525
Asn Val Lys Ile Lys Lys Val Leu Lys Ser Thr Lys Leu Lys Ile Phe	530	535
530	535	540
Arg Gly Lys Arg Thr Leu Tyr Pro Glu Ser Trp Thr Asp Arg Gly Cys	545	550
545	550	555
Thr Cys Pro Ile Leu Asn Pro Gly Leu Glu Tyr Leu Val Ala Gly His	560	565
560	565	570
Glu Asp Ile Arg Thr Gly Lys Leu Ile Val Asn Met Lys Ser Phe Val	575	580
575	580	585
Gln His Trp Lys Pro Ser Leu Gly Arg Lys Val Met Asp Ile Leu Lys	590	595
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Arg Glu Cys Lys	605	610
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615	620	625

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 <212> DNA
 <213> Mouse

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<210> 291

<211> 765

<212> PRT

<213> Mouse

<400> 291

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Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
35          40          45
Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
50          55          60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
65          70          75          80
Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
85          90          95

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Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
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 Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
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 Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
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 Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
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 180 185 190
 Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
 195 200 205
 Ala Ser Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser
 210 215 220
 Gln Thr Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly
 225 230 235 240
 Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly Ala Val Ser Cys
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 Arg Cys Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu
 260 265 270
 Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
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 Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
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 Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
 305 310 315 320
 Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
 325 330 335
 Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
 340 345 350
 Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Arg Asp Glu Leu
 355 360 365
 Leu Asp Asp Gly Glu Glu Gly Glu Asp Glu Glu Glu Pro Trp Glu Asp
 370 375 380
 Phe Asp Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro
 385 390 395 400
 Thr His Pro Pro Asp Phe Gly Leu Pro Tyr Arg Pro Asn Phe Pro Gln
 405 410 415
 Asp Gly Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro
 420 425 430
 Leu Ser Ala Pro Arg Gly Pro Tyr His Ser Ser Val Val Ser Ala Thr
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 Arg Pro Met Val Ile Ser Ala Thr Arg Pro Thr Leu Pro Ser Ala His
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 Lys Thr Ser Val Ile Ser Ala Thr Arg Pro Pro Leu Ser Pro Val His
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 485 490 495
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 500 505 510
 Lys Pro Gly Ile Thr Ser Ala Thr His Pro Ala Arg Ser Pro Pro Tyr
 515 520 525
 Gln Pro Pro Ile Ile Ser Thr Asn Tyr Pro Gln Val Phe Pro Pro His
 530 535 540
 Gln Ala Pro Met Ser Pro Asp Thr His Thr Ile Thr Tyr Leu Pro Pro
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<210>	292
<211>	3020
<212>	DNA
<213>	Mouse

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<210> 293

<211> 266

<212> PRT

<213> Mouse

<400> 293

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          20          25          30
Ser Ser Ile Val Ser Arg Phe Leu Asn Gly Arg Phe Glu Asp Gln Tyr
 35          40          45
Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile His Gly
 50          55          60
Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
 65          70          75          80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
          85          90          95
Val Phe Ser Leu Asp Ser Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
          100          105          110
Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
          115          120          125
Glu Ala Ala Glu Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His
          130          135          140
Ser Glu Leu Cys Arg Gln Val Pro Ala Met Glu Ala Glu Leu Leu Val
          145          150          155          160
Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
          165          170          175
Thr Asn Val Asn Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
          180          185          190
Pro His Glu Met Ser Pro Ala Leu His His Lys Ile Ser Val Gln Tyr
          195          200          205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Thr Lys Val
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Ala Gly Ala Tyr Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val
          225          230          235          240
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<210> 294
 <211> 5520
 <212> DNA
 <213> Mouse

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<210> 297

<211> 500

<212> PRT

<213> Mouse

<400> 297

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Asp Ser Ala Trp Thr Ala Lys Arg Thr Arg Gln Gly Trp Ser Arg Arg
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Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
50 55 60
Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
65 70 75 80
Asn Arg Thr Arg Val Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
85 90 95
Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
100 105 110
Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
115 120 125
Ser His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe
130 135 140
Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
145 150 155 160
Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
165 170 175
Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
180 185 190
Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
195 200 205
Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala

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210	215	220
Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro		
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Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly		240
	245	250
Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu		255
	260	265
Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser		270
	275	280
Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr		285
	290	295
Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr		300
305	310	315
Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe		320
	325	330
Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala		335
	340	345
Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala		350
	355	360
Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser		365
	370	375
Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu		380
385	390	395
Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys		400
	405	410
Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu		415
	420	425
Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser		430
	435	440
Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro		445
	450	455
His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr		460
465	470	475
Tyr Thr Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe Val Glu		480
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Ala Glu Gln Cys		495
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<210> 298
 <211> 2010
 <212> DNA
 <213> Mouse

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<210> 299

<211> 530

<212> PRT

<213> Mouse

<400> 299

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			20				25					30	
Gly	His	His	Thr	Asn	Asp	Trp	Ile	Tyr	Glu	Val	Thr	Asn	Ala
			35				40					45	
Trp	Asn	Glu	Glu	Gly	Val	Glu	Val	Asp	Ser	Gln	Ala	Tyr	Asn
			50				55				60		
Trp	Lys	Arg	Asn	Val	Asp	Pro	Phe	Lys	Ala	Val	Asp	Thr	Asn
			65				70				75		80
Ser	Met	Gly	Gln	Ala	Ser	Pro	Glu	Ser	Lys	Gly	Phe	Thr	Asp
			85				90						95
Leu	Asp	Asp	Gly	Gln	Asp	Asn	Asn	Thr	Gln	Ile	Glu	Glu	Asp
			100				105						110
His	Asn	Tyr	Tyr	Ile	Ser	Arg	Ile	Tyr	Gly	Pro	Ala	Asp	Ser
			115				120						125
Arg	Asp	Leu	Trp	Val	Asn	Ile	Asp	Gln	Met	Glu	Lys	Asp	Lys
			130				135						140
Ile	His	Gly	Ile	Leu	Ser	Asn	Thr	His	Arg	Gln	Ala	Ala	Arg
			145				150						155
Leu	Ser	Phe	Asp	Phe	Pro	Phe	Tyr	Gly	His	Phe	Leu	Asn	Glu
			165				170						175
Val	Ala	Thr	Gly	Gly	Phe	Ile	Tyr	Thr	Gly	Glu	Val	Val	His
			180				185						190
Leu	Thr	Ala	Thr	Gln	Tyr	Ile	Ala	Pro	Leu	Met	Ala	Asn	Phe
			195				200						205
Ser	Val	Ser	Arg	Asn	Ser	Thr	Val	Arg	Tyr	Phe	Asp	Asn	Gly
			210				215						220
Leu	Val	Val	Gln	Trp	Asp	His	Val	His	Leu	Gln	Asp	Asn	Tyr
			225				230						235
Gly	Ser	Phe	Thr	Phe	Gln	Ala	Thr	Leu	Leu	Met	Asp	Gly	Arg
			245				250						255
Phe	Gly	Tyr	Lys	Glu	Ile	Pro	Val	Leu	Val	Thr	Gln	Ile	Ser
			260				265						270
Asn	His	Pro	Val	Lys	Val	Gly	Leu	Ser	Asp	Ala	Phe	Val	Val
			275				280						285
Arg	Ile	Gln	Gln	Ile	Pro	Asn	Val	Arg	Arg	Arg	Thr	Ile	Tyr

290	295	300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val		
305	310	315
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Gly Cys Gly Pro		
	325	330
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu		
	340	345
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp		
	355	360
Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys		
	370	375
Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Thr Ser His Thr Thr		
385	390	395
Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser		
	405	410
Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu		
	420	425
His Leu Lys Asp Ser Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys		
	435	440
Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu		
	450	455
Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His		
465	470	475
His Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser		
	485	490
Arg Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr		
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Ala Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu		
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Gln Cys		525
530		

<210> 300
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 <212> DNA
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<210> 301

<211> 562

<212> PRT

<213> Mouse

<400> 301

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Gly Gly Pro Ala Cys Tyr Gly Gly Phe Asp Leu Tyr Phe Ile Leu Asp
35      40      45
Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
50      55      60
Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
65      70      75      80
Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
85      90      95
Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
100     105     110
Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
115     120     125
Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
130     135     140
Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
145     150     155     160
Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
165     170     175     180
Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
180     185     190
Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
195     200     205
Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
210     215     220
Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
225     230     235     240
Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
245     250     255
Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
260     265     270
Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
275     280     285
Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
290     295     300
Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
305     310     315     320
Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
325     330     335
Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
340     345     350
Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Gly Leu
355     360     365
Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
370     375     380

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Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
 385 390 395 400
 Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
 405 410 415
 Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
 420 425 430
 Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
 435 440 445
 Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
 450 455 460
 Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
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 Ser Val

<210> 302
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 <212> DNA
 <213> Mouse

<400> 302
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<210> 303

<211> 162

<212> PRT

<213> Mouse

<400> 303

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			20					25				30		
Asn	Leu	Arg	Leu	Asp	Cys	Arg	His	Glu	Asn	Asn	Thr	Lys	Asp	Asn
		35					40					45		Ser
Ile	Gln	His	Glu	Phe	Ser	Leu	Thr	Arg	Glu	Lys	Arg	Lys	His	Val
	50					55					60			Leu
Ser	Gly	Thr	Leu	Gly	Ile	Pro	Glu	His	Thr	Tyr	Arg	Ser	Arg	Val
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Leu	Ser	Asn	Gln	Pro	Tyr	Ile	Lys	Val	Leu	Thr	Leu	Ala	Asn	Phe
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Thr	Lys	Asp	Glu	Gly	Asp	Tyr	Phe	Cys	Glu	Leu	Gln	Val	Ser	Gly
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Asn	Pro	Met	Ser	Ser	Asn	Lys	Ser	Ile	Ser	Val	Tyr	Arg	Asp	Lys
		115					120					125		Leu
Val	Lys	Cys	Gly	Gly	Ile	Ser	Leu	Leu	Val	Gln	Asn	Thr	Ser	Trp
	130					135					140			Met
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<210> 304

<211> 4588

<212> DNA

<213> Mouse

<400> 304

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<210> 305

<211> 1479

<212> PRT

<213> Mouse

<400> 305

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35      40      45
Gly Met Gln Gly Cys Leu Glu Ala Gln Gly Val Gln Val Arg Val Thr
50      55      60
Pro Phe Cys Asn Ala Ser Leu Pro Ala Gln Arg Trp Lys Trp Val Ser
65      70      75      80
Arg Asn Arg Leu Phe Asn Leu Gly Ala Thr Gln Cys Leu Gly Thr Gly
85      90      95
Trp Pro Val Thr Asn Thr Thr Val Ser Leu Gly Met Tyr Glu Cys Asp
100      105      110
Arg Glu Ala Leu Ser Leu Arg Met Ala Val Ser Tyr Thr Arg Gly Pro
115      120      125
Val Val Pro Ala Ser Gly Gly Ser Cys Lys Gln Cys Ile Gln Ala Trp
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His Leu Glu Arg Gly Asp Gln Thr Arg Ser Gly His Trp Asn Ile Tyr
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Gly Ser Glu Glu Asp Leu Cys Ala Arg Pro Tyr Tyr Glu Val Tyr Thr
165      170      175
Ile Gln Gly Asn Ser His Gly Lys Pro Cys Thr Ile Pro Phe Lys Tyr
180      185      190
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195      200      205
His Leu Trp Cys Ala Thr Thr Gln Asp Tyr Gly Lys Asp Glu Arg Trp
210      215      220
Gly Phe Cys Pro Ile Lys Ser Asn Asp Cys Glu Thr Phe Trp Asp Lys
225      230      235      240
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Thr Gly Tyr Ser Ser Thr Leu Trp Ile Gly Leu Asn Asp Leu Asp Thr
290      295      300
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325      330      335
Ile Arg Thr Glu Ser Ser Gly Gly Trp Gln Asn His Asp Cys Ser Ile
340      345      350
Ala Leu Pro Tyr Val Cys Lys Lys Lys Pro Asn Ala Thr Val Glu Pro
355      360      365
Ile Gln Pro Asp Arg Trp Thr Asn Val Lys Val Glu Cys Asp Pro Ser
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 35 40 45
 Gly Gly Ser His Glu Val Arg Ser Ser Arg Pro Ala Trp Pro Thr Trp
 50 55 60
 Gln Asn Cys Leu Tyr
 65

PEM's
complete web table # 25 (PEM3) + # 47 (PEM6) are G1, rest are G3

Table 1. Previously characterized and novel Pan Endothelial Markers. The most abundant tags derived by summing the tags from Normal EC (N-EC's) and Tumor EC (T-EC's) SAGE libraries are listed in descending order. N-EC and T-EC SAGE libraries contained 96,694 and 98,688 SAGE tags respectively. For comparison, the corresponding number of SAGE tags found in cultured human umbilical vein endothelial cells (HUVEC), human dermal microvascular endothelial cells (HMVEC), and non-endothelial cell lines (Cell Lines) are shown. The HUVEC SAGE library contained 280,000 tags and the HMVEC library 111,000 tags. Non-endothelial cell lines consisted of 1.8x10⁶ tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. The sequence CATG precedes all tags and the 15th base (11th shown) was determined as previously described by Velculescu et al. (Nat Genet 1999 Dec;23(4):387-8).

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	CATATCATTA	247	501	130	87	2	angiomodulin (ANG), IGFBP-7, IGFBP-rP1, Mac25, TAF
2	TGCACCTCAAG	328	141	0	0	0	hevin
3	TTTGACCTTT	165	84	191	115	4	connective tissue growth factor (CTGF, IGFBP-rP2)
4	CCCTTGTCGG	131	104	1	1	0	ESTs
5	TTGCTGACTTT	73	131	2	14	1	collagen, type VI, alpha 1
6	ACCATTTGGATT	102	67	0	0	2	interferon induced transmembrane protein 1 (9-27, Leu 13)
7	ACACTTCTTTC	104	44	60	62	2	guanine nucleotide binding protein 11
8	TTCTGCTCTTG	71	67	118	72	0	von Willebrand factor
9	TCCCTGGCAGA	66	68	3	13	3	cysteine-rich protein 2 (CRP-2, ESP-1, SmLM)
10	TAATCCTCAAG	28	106	34	16	1	collagen, type XVIII, alpha 1
11	ATGCTTTTCT	58	65	17	17	3	insulin-like growth factor-binding protein 4
12	GGGATTAAAGC	40	67	30	14	2	CD146 (S-Endo 1, P-1H12, Muc18, MCAM, Mel-CAM)
13	TTAGTGTCGTA	38	69	9	13	0	SPARC (osteonectin, BM-40)
14	TTCTCCCAAT	20	86	16	64	2	collagen, type IV, alpha 2
15	GTGCTAAGCGG	24	74	0	10	2	collagen, type VI, alpha 2
16	GTTTATGGATA	35	58	11	11	1	matrix Gla protein (MGP)
17	CCCTTTCACAC	52	33	0	0	0	ESTs, Weakly similar to HPBRII-7 protein
18	TGTTCTGGAGA	58	27	18	56	2	gap junction protein, alpha 1, 43kD (connexin 43)
19	AAGATCAAGAT	34	50	2	4	1	actin, alpha 1, skeletal muscle / actin, alpha 2; smooth muscle, aorta
20	TCTCTGAGCAT	32	48	0	0	0	aggrucanase 1 (metalloproteinase with thrombospondin type 1 motifs, 4)
21	CAGGTTTCATA	22	56	0	0	0	small inducible cytokine subfamily B (Cys-X-Cys), member 14 (BRAX)
22	GCACAAATTCT	43	26	6	22	0	calliconin receptor-like receptor activity modifying protein 2
23	AGCTTGTTGCC	45	23	0	0	0	calliconin receptor-like receptor activity modifying protein 3
24	CTTCTGGATA	13	54	12	0	0	cell division cycle 42 (GTP-binding protein, 25kD)
25	CAACAATAATA	42	25	13	6	0	ESTs

G1

26	ACCGGCGCCCG	50	15	0	0	0	0	tetranectin (plasminogen-binding protein)
27	GGAAGCTAAGT	35	27	0	5	1	0	osteoblast specific factor 2 (fascilin like)
28	GCAATTTAACC	38	21	0	3	0	0	solute carrier family 21 (prostaglandin transporter), member 2
29	GATAACTACAT	18	35	4	4	0	0	angiomodulin (ANG, IGFBP-7, IGFBP-7P1, Mac25, TAF)
30	TATGAGGGTAA	19	30	40	2	0	0	regulator of G-protein signalling 5
31	CCACGGGATTC	10	39	0	0	0	0	collagen, type III, alpha 1
32	TTTACAAAGAG	26	21	0	1	1	1	carboxypeptidase E
33	CCCAGTAAGAT	22	25	0	16	1	1	cysteine and glycine-rich protein 2 (LIM domain only, smooth muscle)
34	ACAAAGCATT	26	20	0	14	1	1	Human insulin-like growth factor binding protein 5 (IGFBP5) mRNA
35	GCCTGTCCCTC	8	38	22	11	0	0	ESTs / biglycan
36	TACTTTATAAG	25	21	1	1	0	0	metalloproteinase with thrombospondin type 1 motifs (ADAMTS1, METH-1)
37	TGTTTAATACA	15	29	2	1	1	1	ESTs / erythrocyte membrane protein band 4.1-like 2
38	GTCCCTGCCTT	18	25	1	1	0	0	glutathione S-transferase M2 (muscle)
39	GAGCCATCATA	21	21	2	2	1	1	ESTs / GTP-binding protein overexpressed in skeletal muscle
40	GGCCCTACAGT	26	13	2	3	0	0	ESTs / KIAA0821 protein
41	GCTAACCCCTG	7	31	0	1	0	0	ESTs
42	ATCACACAGCT	19	18	0	0	0	0	thyroid and eye muscle autoantigen D1 (84kD)
43	ACAAGTACTGT	18	19	36	0	0	0	cadherin 5, VE-cadherin (vascular epithelium)
44	TCACCGTGGAC	20	17	0	1	0	0	selectin P (granule membrane protein 140kD, antigen CD62)
45	ACATTCCAAGT	18	18	0	1	1	1	tissue inhibitor of metalloproteinase 3
46	GAGCCTGGATA	6	29	0	0	0	0	chondroitin sulfate proteoglycan 4 (melanoma-associated)
47	GGCACTCCTGT	22	13	19	12	0	0	ESTs
48	TCACAGCCCCC	20	15	8	5	0	0	ESTs
49	TGCCAGGTGCA	10	23	0	1	0	0	albumin
50	TGGGAAACCTG	11	22	0	1	1	1	eukaryotic translation initiation factor 4 gamma, 1
51	TTTCATCCACT	20	13	0	2	0	0	ESTs, KIAA0362 protein
52	AACAGGGGCCA	15	18	0	0	1	1	interferon, alpha-inducible protein (clone IFI-8-16)
53	ACTGAAAGAAG	6	26	0	0	1	1	complement component 1, s subcomponent
54	ACCGTTCGTGA	8	24	10	6	0	0	transcription factor 4
55	ATACTATAAT	25	6	12	0	0	0	ESTs
56	TTTGTATAGAA	17	15	4	5	1	1	hect domain and RLD 2
57	GTAATGACAGA	20	11	1	1	1	1	stanniocalcin
58	AATAGGGGAAA	13	19	4	1	0	0	ESTs, KIAA1075 protein
59	GTGCTACTTCT	5	25	2	18	0	0	collagen, type IV, alpha 1
60	CCGGCCCCCTCC	6	24	0	0	1	1	peanut (Drosophila)-like 2
61	TTGAATTGTT	19	10	1	1	0	0	RNA-binding protein gene with multiple splicing
62	CGAGAGTGTGA	22	6	0	0	0	0	ESTs
63	CCCTGTTTCAGC	14	15	38	24	0	0	tyrosine kinase with IgG and EGF homology domains (Tie)

64	CAGATGGAGGC	18	10	1	9	0	ESTs
65	AGGCTCCTGGC	8	20	0	0	0	ESTs
66	TCTGCTTCTAG	20	8	40	15	0	ESTs
67	GGCTTAGGATG	18	9	10	14	0	ESTs
68	GGTGTGCGG	6	21	0	0	1	ESTs
69	ACAAGTACCCA	5	22	4	5	0	P311 protein
70	CTTCTCTTGAG	18	9	1	4	1	basic transcription element binding protein 1
71	GCTAATAATGT	10	17	0	2	0	KIAA1077 protein
72	TGTGCTTTTTT	10	15	1	4	0	KIAA0758 protein / protein kinase, cAMP-dependent, catalytic, alpha
73	CATCAGGGATC	17	8	0	1	0	Interleukin 1 receptor, type I
74	GCAGCAGCAGC	6	18	0	2	0	T-box 2
75	TGACTGTATTA	13	11	0	0	0	ESTs / amine oxidase, copper containing 3 (vascular adhesion protein 1)
76	GAATGCTCTTG	6	18	0	11	0	gap junction protein, alpha 4, 37kD (connexin 37)
77	GTAGTCTGGA	18	6	0	5	0	ESTs, clone 23698 mRNA
78	TCCCTCTCTC	6	17	0	0	0	peridontal ligament fibroblast protein
79	GGGCAGTGGCT	5	18	12	5	0	ESTs, DKFZP586B0621 protein
80	AAATATGTGT	19	4	13	3	0	ESTs
81	GTCATTTTCTA	11	11	10	2	0	transcription factor 8 (represses interleukin 2 expression)
82	CTCTCCAAACC	14	8	0	0	0	complement component 1 inhibitor (angioedema, hereditary)
83	TTAATGTGTAA	4	18	0	0	0	guanylate cyclase 1, soluble, beta 3
84	TCAAGCAATCA	13	9	0	1	0	ESTs
85	GAAGACACTTG	15	7	1	0	0	ESTs
86	GGTAGGGTGA	6	15	0	0	1	Integrin, alpha 7
87	TGGAACAGTGA	10	10	10	5	0	ESTs
88	GAGTGGCTACC	10	9	0	0	0	ESTs
89	GTCAGGGTCCC	13	7	0	9	0	decidual protein induced by progesterone
90	GTCAGTCACTT	14	8	4	1	0	hairy (Drosophila)-homolog
91	AGCAGAGACAA	14	6	1	10	0	natriuretic peptide receptor A - guanylate cyclase A
92	AGCGATGGAGA	9	10	0	0	0	ESTs
93	CGTGGGGTGA	9	10	17	3	0	

TEM's complete web table

Table 2. SAGE tags elevated in tumor endothelium. The top 46 tags with the highest tumor EC (T-EC's) to normal EC (N-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parentheses. †: multiple tags for this gene are due to alternative polyadenylation sites.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	GGGGCTGCCCA	0	28	0	2	0	ESTs, similarly to thrombomodulin
2	GATCTCCGTGT	0	25	0	0	0	ESTs, similarly to rat Rhes ras-related protein
3	CATTTTATCT	0	23	0	0	0	ESTs
4	CTTCTTTGAG	0	22	6	20	1	regulated in glioma-like 7-1 (Dkk-3/ REIC)
5	TATTAACCTC	0	21	1	3	1	ESTs, similarly to JNK interacting protein-3a
6	CAGGAGACCC	0	16	2	0	0	MMP-11 (stromelysin 3)
7	GGAAATGTCAA	1	31	53	22	1	MMP-2 (gelatinase A, 72kD type IV collagenase)
8	CCTGGTTCAGT	0	15	0	0	0	ESTs
9	TTTTTAAGAAC	0	14	1	4	0	ESTs
10	TTTGGTTTCC	5	139	0	16	0	collagen, type I, alpha 2, transcript A'
11	ATTTTGATGA	0	13	4	8	0	nidogen (entactin)
12	ACTTTAGATGG	1	23	0	15	0	collagen, type VI, alpha 3
13	GAGTGAGACCC	3	63	0	0	1	Thy-1 cell surface antigen
14	GTACACACACC	0	10	0	0	0	ESTs / cystatin S
15	CCACAGGGGAT	2	38	0	2	1	collagen, type III, alpha 1
16	TTAAAGTCCAC	1	19	1	3	1	ESTs
17	ACAGACTGTTA	4	74	0	0	0	ESTs, similarly with sea squirt nidogen
18	CCACTGCAACC	1	18	0	1	0	ESTs, similarly with homeobox protein DLX-3
19	CTATAGGAGAC	1	18	1	1	0	collagen, type I, alpha 2, transcript B'
20	GTTCCACAGAA	0	9	0	3	0	ESTs / pregnancy specific beta-1-glycoprotein 1
21	TACCACCTCCC	0	9	4	1	1	endo180 lectin
22	GCCCTTCTCT	1	17	3	1	2	collagen, type I, alpha 1
23	TAAATAGCAC	2	33	0	4	0	ESTs, DKFZP434G162 protein
24	AGACATACTGA	1	16	1	0	0	bone morphogenetic protein 1 (metalloproteinase)
25	TCCCCCAGGAG	1	16	0	0	0	silk (Drosophila) homolog 3 (MEGF5)
26	AGCCCAAAGTG	0	8	0	0	0	KIAA0672 gene product
27	ACTACCATAAC	0	8	0	0	0	
28	TACAAATCGTT	0	8	0	0	0	

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29	TTGGGTGAAAA	0	8	0	0	0	0	ESTs
30	CATTATCCAAA	0	8	0	0	0	0	integrin, alpha 1
31	AGAAACCCACGG	0	8	2	7	0	0	collagen, type IV, alpha 1
32	ACCAAAACCCAC	0	8	0	3	0	0	
33	TGAAATAAAC	0	8	3	1	1	1	
34	TTTGGTTTCC	1	15	0	0	0	0	ESTs
35	GTGGAGACGGA	1	15	1	2	1	1	ESTs
36	TTTGTGTTGTA	1	14	2	0	0	0	collagen, typeXII, alpha 1
37	TTATGTTTAAAT	3	39	0	0	1	1	lumican
38	TGGAAATGACC	15	179	0	40	0	0	ESTs / collagen, type I, alpha 1
39	TGCCACACAGT	1	13	0	2	0	0	transforming growth factor, beta 3
40	GATGAGGAGAC	3	35	0	18	1	1	collagen, type I, alpha 2, transcript C1
41	ATCAAAGGTTT	2	23	0	0	0	0	ESTs, DKFZp564O222 mRNA
42	AGTCACATAGT	1	11	2	0	0	0	cell division cycle 42 (GTP-binding protein)
43	TTCGGTTGGTC	4	45	0	19	0	0	
44	CCCCACACGGG	2	21	0	0	0	0	ESTs
45	GGCTTGCGTTT	1	10	0	10	1	1	
46	ATCCCTTCGCG	1	10	1	0	0	0	peanut-like protein 1

Table 3. Detection of transcripts in various tumor types by RT-PCR and in situ hybridization (ISH). The "+" sign indicates the presence of a robust RT-PCR product or strong positive staining of vessels by in situ hybridization. The "-" sign indicates an undetectable signal by in situ hybridization or an absent or barely detectable transcript by RT-PCR. The "+/-" sign indicates a very weak signal in a limited number of vessels by in situ hybridization.

	TEM1	TEM3	TEM4	TEM5	TEM7	TEM8	TEM9	vWF	Hevin
RT-PCR	Colon Nor.	-	-	-	-	-	-	+	ND
	Colon Tum.	+	+	+	+	+	+	+	ND
	Colon Nor.	-	-	-	-	-	-	+	+
ISH	Colon Tum.	+	+	+	+	+	+	+	+
	Liver Met.	+	+/-	+	+	+	+	+/-	ND
	Lung Tum.	+	+	+	+	+	+	+	+
	Brain Tum.	+	ND	ND	+	ND	ND	+	+
	Corpus Lut.	+	+	+	+	-	+	+	+
	Wound	+	ND	+	ND	+/-	ND	+	+

* hevin was localized to both endothelial cells and malignant cells in brain tissue.
ND: not determined.

www.sagenet.org/langio/table3.htm (to be posted upon publication)

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Table 3. SAGE tags elevated in normal endothelium. The top 46 tags with the highest normal EC (N-EC's) to tumor EC (T-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	TCTCAGTCT	26	0	0	0	0	mucosal vascular addressin cell adhesion molecule 1
2	CTAGCGTTT	19	0	4	14	0	serum deprivation response (phosphatidylserine-binding protein)
3	GTGGCTGACG	18	0	1	0	0	ESTs / intercellular adhesion molecule 4
4	CTCTTAAAAA	34	1	1	0	0	small inducible cytokine subfamily A (Cys-Cys), member 14
5	TGGGAAGAGG	16	0	3	4	1	ESTs
6	GTTTAAGGAT	16	0	0	0	0	ESTs
7	CTTTGTTTG	15	0	56	32	1	endothelin 1 / ribosomal protein L27
8	ATTGCCAATC	14	0	0	4	0	TU3A protein
9	TGTTGAAAAA	21	1	1	0	0	selectin E (endothelial adhesion molecule 1)
10	ACAAAAGGC	21	1	0	6	0	TU3A protein
11	AAGATGCACAC	21	1	1	1	1	phosphodiesterase 1 - nucleotide pyrophosphatase 2 (autotaxin)
12	GTAGAGGAAA	10	0	0	9	0	platelet/endothelial cell adhesion molecule (CD31 antigen)
13	TTGTTCAAGG	10	0	0	1	0	ESTs
14	CTCTTCAAAAA	19	1	1	0	0	ESTs / small inducible cytokine subfamily A, member 14
15	TATTAAATA	18	1	6	9	1	transforming growth factor, beta receptor II (70-80kD)
16	GAATTCACCA	9	0	1	14	0	ESTs
17	AAGGAGAACT	9	0	0	0	0	small inducible cytokine subfamily A, member 14
18	AATATCTGAC	9	0	2	2	2	active BCR-related gene
19	TCAGTGACCAG	17	1	4	7	2	protein kinase C eta
20	GCAAAGTGCC	32	2	1	5	0	ESTs
21	TAAATACTTG	8	0	2	0	0	ESTs (2 unigene clusters)
22	GTCACATAAT	8	0	1	0	0	ESTs
23	ATAACCTGCA	8	0	0	0	0	signaling lymphocytic activation molecule
24	TGCATCTGTGC	46	3	1	1	0	ESTs / glycogenin 2
25	TAAAGGCACA	15	1	4	3	0	LIM binding domain 2
26	GACCGCGGCT	73	5	11	7	0	claudin 5
27	ACTCCGGTGT	14	1	0	8	0	ESTs

28	CTTCTCACCT	27	2	3	1	0	GTP-binding protein
29	TCGTGCTTTG	13	1	0	0	0	ESTs
30	GAGCAGTGCT	13	1	4	2	1	feline sarcoma viral (v-fes) - Fujinami avian sarcoma viral (v-fps) homolog
31	CTCTAAAAA	10	1	0	1	0	ESTs
32	GAAACCCGGT	10	1	0	0	1	phospholipase C, beta 4
33	AACACAGTGC	10	1	7	15	1	ESTs

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